Pediatric migraine prevention: Current evidence and future directions in the era of calcitonin gene-related peptide

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The following is a review of the current literature focusing on pediatric migraine prevention, with attention to calcitonin gene-related peptide (CGRP) modifying medications. This is presented within the context of a multimodal approach to wellness regarding headache care in pediatrics. Pediatric headache medicine can be challenging, given the lack of research on this topic. In addition, difficulties with designing research protocols, communication limitations and developmental considerations create barriers to obtaining evidence-based outcomes. This is especially concerning given the vulnerability of this population. Through a literature search focusing on preventive headache treatment and CGRP, this article presents current evidence and consensus statements regarding the standard of care in pediatric migraine.

Keywords

Calcitonin gene-related peptide (CGRP), gepants, headache disorders, migraine prevention, monoclonal antibodies, pediatric migraine

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Migraines profoundly impact well-being, especially in children and adolescents. From 1990 to 2021, global pediatric migraine disability has increased, with particular vulnerability in females and adolescents aged 15–19.[1] A 2023 meta-analysis found the prevalence of primary headache diagnosis in individuals aged 8–18 years to be 62%.[2] The prevalence of a migraine diagnosis was 11%; 8% presented as migraine without aura and 3% as migraine with aura.

Epidemiologic data collected regarding pediatric patients with headache may actually underrepresent the true magnitude of disease burden due to comparatively less funding for research. A 2021 analysis of National Institutes of Health funding for pediatric disorders revealed that pediatric headache resulted in the highest measured disability while receiving the least amount of funding.[3] Fortunately, the advent of several new treatment options for migraine disorders has created a surge in pediatric migraine research, especially involving calcitonin gene-related peptide (CGRP).

Living with migraine can cause a severe disease burden in pediatric and adolescent patients, along with impacting the lives of caregivers and family. The presence of headaches in children was associated with decreased school participation, and absences were positively correlated with headache frequency in patients aged 5–19.[4] In addition, patients aged 6–17 years with mood or anxiety disorders have higher reported levels of headache disability.[5] Adolescents aged 12–17 years with headaches are more likely to experience bullying from peers, mood/anxiety disorders and suicidality.[6]

Traditional adult preventive headache therapies, including antidepressants, antiepileptics and antihypertensive medications, were not originally designed to treat migraine.[7] Most were incidentally found to decrease migraine severity and frequency, though side effect profiles were poor. Medicines were dose-adjusted for pediatric patients given the lack of US Food and Drug Administration (FDA)-approved migraine treatments.

Research in pediatric migraine has traditionally involved participants aged 6–18, though children under 6 years can experience migraine as well. This research has identified an unfavorable side effect profile in many pediatric migraine preventive therapies, cultivating interest in alternative treatment avenues. Promising new data on CGRP-related therapeutics in adults now allows for a shift in pediatrics toward CGRP modulation for migraine.

To evaluate the existing evidence for preventative migraine therapy in pediatrics, a literature search was performed via the Primo search engine through institutional access to all journal articles, texts, ebooks and electronic databases. Google Scholar was also used, as well as the American

Headache Society (AHS) and the American Academy of Neurology (AAN) websites to view consensus statements and current publications. This paper presents a summary of this data.

Pediatric migraine prevention before the era of CGRP

The standard of care for pediatric headache prevention involves a stepwise approach that begins with addressing lifestyle factors that contribute to migraine, including adequate sleep, nutrition, hydration and physical activity. In addition, it is recommended to discuss modifying migraine triggers, including the use of electronic devices, alcohol, obesity, substance use and stress.[8]

Following lifestyle modifications, nutraceuticals are often presented as an option, and several have been investigated for potential migraine prevention. However, studies in pediatric patients are limited by low sample sizes and product heterogeneity. There is some evidence for magnesium, vitamin B12 and vitamin D.[9] Currently, there are no evidence based or consensus-based recommendations on the implementation of nutraceuticals in pediatric migraine treatment.[10]

Cognitive-behavioral therapy (CBT) has robust evidence in support of migraine prophylaxis and was demonstrated to enhance the efficacy of preventive treatment with amitriptyline.[11,12] Similarly, biofeedback and relaxation techniques were found to be beneficial in preventing pediatric migraine and can be integrated into a multimodal treatment plan.[13] There is evidence in adults for a behavioral intervention app utilizing guided intervention of education and relaxation in combination with remote electrical neuromodulation (REN) that has demonstrated efficacy as well.[14] REN is an FDA-cleared neuromodulation device that is worn on the upper arm to stimulate peripheral nerves. Other neuromodulation devices that are cleared by the FDA for use in pediatrics include single-pulse transcranial magnetic stimulation and non-invasive vagus nerve stimulators.[15]

There are non-CGRP medications used for the prevention of pediatric migraine (*Table 1*).[15–19] Many were incidentally found to have therapeutic benefits for this condition in adults. In 2019, the AAN and the AHS developed guidelines for the preventive treatment of headaches in children and adolescents. This included antiepileptic medicines such as topiramate and extended-release divalproex sodium (DVPX ER). Topiramate showed moderate confidence in decreased monthly migraine day (MMD), low confidence in decreased migraine-related disability and insufficient evidence in all other outcomes. There was insufficient evidence for DVPX ER. The antidepressant, amitriptyline, was found to have insufficient evidence as a stand-alone treatment.[7]

Table 1: Pediatric non-CGRP preventive pharmaceuticals and neuromodulation devices[15–19]

Drug class	Pharmaceutical name	Dosing	Common side effects
Antiepileptic	Divalproex sodium ER	250 mg/d,500 mg/d, or 1,000 mg/d	Thrombocytopenia and other bone marrow suppression, pancreatitis, hyperammonemic encephalopathy, hepatotoxicity, teratogenic, carnitine deficiency, polycystic ovary syndrome, sedation, weight gain, hair loss, hair curling, dizziness, ataxia, nystagmus, tremor[16,17]
	Topiramate	100 mg/d or 2–3 mg/kg/d	Teratogenic, nephrolithiasis, glaucoma, word-finding, difficulties, weight loss, paresthesia, decreased sweating, decreased efficacy of oral contraceptive pills at doses ≥200 mg/day[16,17]
	Levetricetam**	20–60mg/kg/day (250–3,000 mg/day)	Fatigue, psychiatric and behavioural side effects (irritability, mood lability)[17–19]
Antidepressent	Amitriptyline	1 mg/kg daily	Increased risk of suicidality, increased risk of serotonin syndrome when combined with other medications that increase serotonin, constipation, dry eyes, dry mouth, sedation, QT prolongation[16,17]
	Amitriptyline and CBT	Amitriptyline (1 mg/kg/d)	
Beta-Blocker	Propranolol	20–40 mg, 3 times a day	Hypotension, bradycardia, weight gain, may worsen asthma and depression[16,17]
Calcium Channel Blocker	Flunarizine*	5 mg/d	Sedation, weight gain[16,17]
	Cinnarizine*	1.5 mg/kg/d if <30 kg or 50 mg/d if >30 kg	Sedation, weight gain[16,17]
	Nimodipine	10–20 mg, 3 times a day	Gastrointestinal side effects, hypotension, bradycardia, nausea[16,17]
Antihistamine	Cyproheptadine**	0.04 to 0.2 mg/kg	Sedation, weight gain[17,19]
Neurotoxin	Onabotulinumtoxin A	74 U IM or 155 U IM	Injection-site pain, neck weakness, worsened headache, ptosis[16,17]

Device class	Device name	Age group	Application site	Common side effects
Neuromodulation Devices**	Single pulse transcranial magnetic stimulation (s-TMS)	12+	Back of the head	Light headedness, tingling, tinnitus, dizziness[15]
	Non-invasive vagus nerve stimulator (nVNS)	12+	Side of the neck	Application site discomfort, irritation, redness, tingling, prickling; muscle twitching and/or contractions; pain in face, head, neck, teeth, dizziness[15]
	Remote electrical neuromodulation (REN)	8+	Upper outer arm	Warmth, temporary arm/hand numbness, itching, tingling, muscle spasm, pain in the arm, shoulders, neck, rash or redness at site[15]

** not available in the USA*
*** not part of recommendations from 2019 AAN and AHS Guidelines*
CGRP = calcitonin gene-related peptide.

The pivotal Child and Adolescent Migraine Prevention (CHAMP; ClinicalTrials.gov identifier: NCT01581281) trial compared the frequency of headache and headache disability when treated with amitriptyline, topiramate or placebo.[20] The primary outcome was the 'reduction of 50% or more in the number of headache days.' There were no significant differences found between treatment groups, with 52% of the amitriptyline group, 55% of the topiramate group and 61% of the placebo group attaining the primary outcome. Notably, adverse events were more common with amitriptyline and topiramate compared with placebo.

In combination with CBT, however, amitriptyline showed high confidence in decreased MMDs, 50% reduction in headache frequency and moderate confidence in decreased migraine-related disability. The β-blocker, propranolol, showed low confidence in a 50% reduction in headache frequency. Calcium channel blockers assessed included flunarizine, cinnarizine, and nimodipine. Flunarizine and nimodipine had insufficient evidence. However, cinnarizine had moderate confidence in decreased MMD and headache severity, but it is not available in the USA. OnabotulinumtoxinA, a neurotoxin, was determined to have insufficient evidence; however, the pivotal trial involved only one treatment dose.[7] Adult trials showed that at least two treatments were necessary to demonstrate efficacy.[21]

It should be noted that preventive treatment medications should be used in conjunction with acute therapies such as triptans, non-steroidal anti-inflammatory drugs (NSAIDs), neuromodulation devices and more for optimal care.[15,22] This article focuses on preventive treatment options for the pediatric population, as this landscape is rapidly changing.

CGRP therapies have demonstrated success and favorable side effect profiles in adults for both prevention and acute treatment, making them an attractive option for pediatrics. These have been used off-label for pediatric patients who have not been adequately supported by traditional, pharmaceutical treatments.[23]

The CGRP pathway in migraine pathophysiology

The neuropeptide, CGRP, was first discovered in 1982. The involvement of CGRP in migraine pathophysiology was first proposed in 1985 and was confirmed in 1990. First discovered in the 1980s and marketed in the 1990s, triptans target the presynaptic receptors to regulate CGRP release. These medications have been utilized in the acute treatment of migraine. In 2000, a group of small peptide receptor antagonists referred to as gepants was first characterized for their affinity for CGRP receptors. These medications are designed to be taken by mouth. In 2004, olcegepant, the first gepant discovered, demonstrated acute relief of migraine. Several other gepants were evaluated for acute migraine therapeutics, but trials ceased as concerns for hepatotoxicity rose. In 2013, large molecule monoclonal antibodies (mAbs) for prophylactic migraine treatment gained interest. These medications are designed to be delivered intravenously or through subcutaneous injection monthly or quarterly. These antibodies are not processed by the liver, mitigating the risk for hepatotoxicity. Additionally, mAbs have a long serum half-life, relieving the need to take the medication frequently. Furthermore, the antibodies have high affinity and selectivity for CGRP receptors, reducing off-target side effects. Recent clinical trials involving several gepants, including ubrogepant, rimegepant and atogepant, have demonstrated preventive and acute migraine relief without concern for hepatotoxicity or other serious adverse effects. While gepants lack a prolonged half-life, their oral formulation addresses concerns about injection-site reactions with administration of mAbs.[24]

In 1990, the involvement of CGRP in migraine pathophysiology was confirmed in adults through observed elevated CGRP release during migraine attacks.[24] Recent pediatric studies show that mean plasma levels of CGRP are elevated in migraine patients both ictal and in interictal periods, compared with patients with non-migrainous headaches. Young patients with high-frequency migraine also had higher CGRP levels compared with those with low frequency.[25] Additionally, CGRP levels have been shown to decrease throughout the lifespan.[24]

Evidence for CGRP-targeted therapies in adults

Multiple CGRP therapies have undergone preventive clinical trials in adults. These trials are traditionally divided to account for the number of monthly headache/migraine days; therefore, patients are classified as chronic (≥15 headache days per month) or episodic (<15).[26] Current FDA-approved anti-CGRP preventive options include mAbs: erenumab, fremanezumab, galcanezumab, eptinezumab and gepants: rimegepant and atogepant. All therapies have demonstrated reductions in MMDs for adults in 12–28 week clinical trials, along with proven safety and tolerability in long-term investigations. These treatments are listed in *Table 2*, highlighting pivotal trials regarding primary outcomes, route of delivery, as well as safety and efficacy.[19,27–46] All mAbs and the gepant atogepant are approved for both episodic and chronic migraine. However, the gepant rimegepant is only approved for episodic migraine.[47]

In 2024, the AHS issued a position statement endorsing CGRP therapy for migraine prevention as effective, safe and tolerable. They recommended CGRP therapies as a 'first-line treatment' for adults that 'should not require trial and failure of non-specific migraine preventive medication approaches.' The statement emphasizes the low dropout rate in clinical trials, indicating adherence. Furthermore, the AHS not only discussed the positive results from clinical experience with off-label use of CGRP therapies but also acknowledged the paucity of evidence in pediatrics.[47]

Emerging data in the pediatric populations

A small retrospective study evaluated the effectiveness and tolerability of anti-CGRP therapeutics (including erenumab, eptinezumab, fremanezumab, galcanezumab, rimegepant, ubrogepant and atogepant) in patients aged 12–21 for headache. After 1 month, 82.6% experienced >50% reduction in headache days. Satisfaction was reported by 69.89% of patients, with 95.7% reported no side effects and 69.9% continued treatment. Authors noted increased effectiveness when anti-CGRP therapeutics were combined with OnabotulinumtoxinA or other traditional therapies. However, this was a very small sample size (n=23) with heterogeneous treatment.[48]

Fremanezumab attained FDA approval for migraine in pediatric patients in August 2025 and is currently the only FDA-approved CGRP treatment for pediatric migraine.[49] The medication is delivered through a subcutaneous injection monthly, and it is approved for patients aged 6–17, over 45 kg, with episodic migraine only. In the clinical trial, 47.2% of participants on fremanezumab experienced a 50% or greater reduction in MMDs, compared with 27% control. The most common adverse event was injection site erythema, in 9.8% of the treatment group and 5.4% placebo. Patients received 120 mg for <45 kg and 225 mg for ≥45 kg. However, commercially available fremanezumab is only available at a 225 mg dosage.[49,50] There is currently no FDA-approved anti-CGRP therapeutic for pediatric patients <45 kg, <6 years old or with chronic migraine. However, it is important to note that there are several ongoing pediatric clinical trials researching additional anti-CGRP therapeutics, which are described in *Table 3*.[50–65] These medications were approved for adults.

Table 2: Adult CGRP preventive treatments – FDA approved[27–46]

Drug class	Pharmaceutical name	Route of delivery/ Frequency	Dose	EM/CM	Primary outcome	Side effects
Monoclonal Antibody	Erenumab	SC Injection monthly	70 mg, 140 mg[27]	EM	MMD	Constipation, injection site reactions, URI, nasopharyngitis, hypertension, Raynauds phenomenon, nausea, UTI, influenza, sinusitus, arthralgia, migraine, diarrhea, fatigue, bronchitis
			70 mg[28]	CM	MMD	
			70 mg[29]	EM	MMD	
			70 mg, 140 mg[30]	EM	MMD	
	Fremanezumab	SC Injection monthly or quarterly	225 mg, 675 mg[31–33]	EM	MMD	Injection site reactions, URI, nasopharyngitis, hypertension, Raynauds phenomenon, sinusitis, bronchitis, migraine, UTI, influenza
				CM	MHD	
				EM and CM	Safety and tolerability	
	Galcanezumab	SC Injection monthly	120 mg, 240 mg[34–3745–47]	EM and CM	Safety and tolerability	Injection site reactions, URI, nasopharyngitis, hypertension, Raynauds phenomenon, sinusitis, weight gain, back pain, nausea, arthralgia, influenza, dizziness, myalgia
				EM	MMD	
				EM	MMD	
				CM	MMD	
	Eptinezumab	IV quarterly	100 mg, 300 mg[38]	CM	MMD	Hypertension, Raynauds phenomenon, hypersensitivity, fatigue
			30 mg, 100 mg, 300 mg [39]	EM	MMD, MRR, short term medication use	
			30 mg, 100 mg, 300 mg[40]	EM	MMD	
			300 mg[41]	CM	Safety and tolerability	
Gepant	Atogepant	PO BID or QD	30 mg, 60 mg[42]	CM	MMD	Constipation, injection site reactions, URI, nasopharyngitis, hypertension, Raynauds phenomenon, weight loss, gastroenteritis, elevated AST, fatigue, anxiety, dizziness, nausea, anxiety, sinusitus, arthralgia, muscle strain, pharyngitis streptococcal
			10 mg, 30 mg, 60 mg[43]	EM	MMD	
			60 mg[44]	EM	Safety and tolerability	
	Rimegepant	PO EOD	75 mg[45,46]	EM and CM	MMD	Nasopharyngitis, URI, nausea, UTI, hypertension, Raynauds phenomenon
				EM and CM	MMD	

AST = aspartate aminotransferase; BID = twice daily; CM = chronic migraine; EM = episodic migraine; EOD = every other day; IV = intravenous; MHD = monthly headache days; MMD = monthly migraine days; MRR = migraine responder rates; PO = by mouth; QD = daily; SC = subcutaneous; URI = upper respiratory tract infection; UTI = urinary tract infection.

Clinical and ethical considerations

As seen in the CHAMP trial, pediatric patients have elevated placebo rates, creating challenges with clinical trials.[20] In 2018, the AHS Pediatric and Adolescent Headache special interest group (SIG) issued recommendations on anti-CGRP mAbs in children and adolescents, at a time when no anti-CGRP mAbs were approved for pediatrics. Within the recommendations, the SIG discussed trial design and participant selection. Trial design for pediatric patients included a single-blind placebo run-in, as well as a crossover design. Further recommendations emphasize the inclusion of patients with continuous headaches along with those who have not responded to prior therapies. Additional suggestions include monitoring growth and long-term follow-up.[66]

CGRP is involved in several physiological processes; therefore, there has been concern for CGRP therapies in developing patients. Animal models suggest that CGRP plays a role in bone ossification and formation, as demonstrated by decreased bone mass when the α-CGRP gene is knocked out. There is limited evidence in humans; however, caution is advised for patients with bone diseases, as well as osteopenia. Additionally, growth should be monitored while utilizing mAbs in developing patients, as 90% of peak bone mass is achieved by age 18. Providers may consider only prescribing to post-pubertal patients and supplementing vitamin D. Weight and body mass index (BMI) should also be monitored due to mAbs' potential impact on metabolism, as high CGRP levels have been linked to obesity. Therefore, it has been theorized that mAbs may decrease body weight.[66] There are currently no long-term prospective studies evaluating bone health in adult or pediatric patients on CGRP inhibitors.

CGRP and its receptors are also involved in brain development and central nervous system maturation. Anti-CGRP mAbs do not cross

Table 3: Pediatric CGRP preventive studies[50–65]

Drug class	Pharmaceutical name	Dosing	Age (in years)	EM/CM	Primary outcome	Side effects
Monoclonal antibody	Fremanezumab	120 mg<45 kg and 225 mg≥45 kg	6–17[50]	EM	MMD	Injection site erythema, pain, and swelling
			6–17[51]	CM	MMD	Injection site erythema, upper abdominal pain, injection site induration, neutrophil count decrease, increased prothrombin international normalized ratio, prothrombin time prolonged and laceration.
			6–17[52]	EM and CM	Safety and tolerability	
	Erenumab	35–70 mg<40 kg and 70–140 mg≤40 kg	6–17[53]	EM	MMD	Respiratory tract infection, headache, and vomiting.
			6–17[54]	CM	MMD	
	Galcanezumab	120 mg/mL, 1 mL every 30 days	12–17[55]	CM	MMD	Constipation and fatigue.
			6–17[56]	EM	MMD	
	Eptinezumab	150 mg>20kg≤40 kg, 300 mg>40 kg	6–17[57]	EM	MMD	Orthostatic hypotension and infusion related reactions.
			6–17[58]	EM and CM	TEAEs	
			12–17[59]	CM	MMD	
Gepant	Atogepant	Oral Tablet	12–17[60]	CM	AEs, MMDs	No data in paediatrics patients.
			6–17[61]	EM	MMDs	
			6–17[62]	EM and CM	AEs	
	Rimegepant	75 mg, 50 mg or 35 mg	6–17[63]	EM and CM	AEs	No data in paediatric patients
		75 mg or 50 mg (2×25 mg)	6–17[64]	EM	MMDs	
		75 mg	12–17[65]	CM	MMDs	

AEs = adverse effects; CGRP = calcitonin gene-related peptide; CM = chronic migraine; EM = episodic migraine; MMD = monthly migraine days; TEAEs = treatment emergent adverse effects.

the blood–brain barrier, but their use should be limited in pediatric patients with damaged blood–brain barriers. CGRP is present in both the cardiovascular system and the perivascular nerves, raising concern about the potential cardiovascular effects of CGRP-related therapeutics. The pivotal trials involving CGRP-targeted medications have not revealed serious medication-related adverse events that were cardiovascular in nature. However, the FDA updated prescribing information for all CGRP-targeted migraine medications warning that hypertension can develop or worsen and Raynaud's phenomenon can develop or worsen when taking these medications.[67] Similarly, concerns have arisen about the effect of blocking CGRP in the immune system, given the role of CGRP in the neuro-immune axis. The lack of serious infections in adult trials has mitigated this concern.[66]

Given concerns of low adherence to medical treatment and high placebo effect in pediatric populations, it is important to address both caregiver and patient openness to treatment. Both female patients and their caregivers demonstrated greater openness to treatment. Caregivers with education extending beyond high school were more open to treatment.[68] The mosaic of factors that impact openness to treatment must be considered and discussed between family and clinician to foster trust, ultimately promoting the care plan.

In adult patients, socioeconomic factors and race were found to significantly affect prescription access to CGRP therapeutics, as White participants were most likely to receive these medicines.[69] It remains unclear how disparities in headache care may impact access to emerging treatments, such as mAbs and gepants, for pediatric patients, as the majority of these medications are still used off-label. These formulations are also relatively expensive, which causes insurance coverage issues.[68] Clearly, further research and accessibility are necessary to provide optimal care for all patients.

Practical implications for clinical practice

In the 2018 recommendations, the Pediatric and Adolescent Headache SIG suggested considering anti-CGRP mAbs for pediatric patients with ≥8 MMD and moderate-to-severe disability measured by PedMIDAS or another validated instrument. They recommended 2–3 other preventive treatments trialed prior to anti-CGRP use. When treating developing patients, trial treatment at the lowest dose for 2 months and increase if necessary. Once a therapeutic goal is attained for a few months, the patient could eventually attempt to wean off the medication in the future, as pediatric migraine may have a shorter natural course in some patients.[66]

Each individual patient requires a unique treatment plan to meet their specific needs. This may often involve a multimodal treatment approach; however, there are few studies that evaluate combined preventive therapies with CGRP products in the pediatric population. A small retrospective study (n=10) evaluated the efficacy of anti-CGRP interventions in combination with lifestyle modifications in pediatric patients with chronic migraines. Lifestyle modifications were classified as exercise, sleep and nutrition. Over the 12-month study period, migraine disability, migraine frequency and rescue medication use decreased, suggesting the need for further investigations.[70]

There is currently a lack of empirical evidence on the combination of nutraceuticals, behavioral interventions, neuromodulators, preventive pharmaceuticals and acute pharmaceuticals in conjunction with CGRP therapeutics in children. However, there is evidence for the benefits of combination therapy in adults. Notably, there is strong evidence for the prophylactic treatment of migraine with CGRP-targeting therapies combined with OnabotulinumtoxinA treatments in adults. Additionally, non-CGRP targeting therapeutics are a relatively accessible therapy that can provide added benefit for migraine relief when used in combination with CGRP targeting therapeutics.[71] While these data provide meaningful insight into

treating pediatric headache disorders, further research may emerge with future access to FDA-approved preventive treatment in pediatrics.

Future directions

There are currently several clinical trials in progress to assess anti-CGRP therapeutics for both preventive and acute treatment of migraine headaches, as seen in *Table 3*. Given our current understanding of CGRP's role in migraine pathophysiology, this has become a possible biomarker of interest; however, studies show variable results.[25] Additionally, longitudinal investigations on CGRP-targeting therapies in pediatric patients with particular attention to developmental concerns, including bone health and cardiovascular changes, are needed. Considerations should be made for sex differences, particularly in patients of childbearing age. Current practice parameters for the preventive treatment of pediatric headache do not include CGRP-related therapies. The development of updated guidelines with the addition of these treatment options is essential as clinical trials conclude. Barriers in access to these medications due to approval and socioeconomic factors also require significant attention.[71] FDA approval of such medications may support mitigating these barriers.

Conclusion

Treatment of headache in children and adolescents necessitates a multifactorial approach and has historically been overlooked and underresearched. However, with the advent of CGRP-directed therapeutics in adult migraine, there has been a noticeable rise in dedicated pediatric migraine research. This article discusses the most up-to-date literature on pediatric migraine prevention, focusing on the emerging use of CGRP treatments and evidence-based standards of care. Anti-CGRP therapies are extremely promising for pediatrics due to their demonstrated efficacy and low side effect profile. However, studies are limited by challenges with design protocols for pediatric populations, as well as concerns regarding development and dosing. Even when medications are successfully FDA approved for pediatric migraine, access remains an issue. Migraine is a disease that affects adults and children alike. Preventive therapy can significantly improve the quality of life for both patients and families and should be appropriately researched and made accessible for all ages. The pediatric migraine horizon continues to show promise, given the many CGRP therapies still in clinical development. ❑

1. Sun Q, Xie H, Hao L, et al. Global epidemiology and burden of migraine in children and adolescents from 1990 to 2021: Insights from the Global Burden of Disease Study 2021. *J Pain Res*. 2025;18:5265–81. DOI: 10.2147/JPR.S542845.
2. Onofri A, Pensato U, Rosignoli C, et al. Primary headache epidemiology in children and adolescents: A systematic review and meta-analysis. *J Headache Pain*. 2023;24:8. DOI: 10.1186/s10194-023-01541-0.
3. Rees CA, Monuteaux MC, Herdell V, et al. Correlation between national institutes of health funding for pediatric research and pediatric disease burden in the US. *JAMA Pediatr*. 2021;175:1236–43. DOI: 10.1001/jamapediatrics.2021.3360.
4. Berring-Uldum AA, Skovgaard LT, Miranda MJ, Debes NM. Education and social life: The impact of headache on participation in children and adolescents attending a headache clinic-a case-control study. *Pediatr Neurol*. 2025;169:185–95. DOI: 10.1016/j.pediatrneurol.2025.05.030.
5. Murphy C, Ladak A, Szperka CL, et al. Anxiety, depression, and headache-related disability in a large pediatric clinic-based sample. *Headache*. 2025;65:420–9. DOI: 10.1111/head.14849.
6. Nilles C, Williams JVA, Patten S, et al. Association between peer victimization, gender diversity, mental health, and recurrent headaches in adolescents: A Canadian population-based study. *Neurology (ECronicon)*. 2023;101:e1654–64. DOI: 10.1212/WNL.0000000000207738.
7. 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. *Neurology (ECronicon)*. 2020;94:50. DOI: 10.1212/WNL.0000000000008750.
8. Raucci U, Boni A, Evangelisti M, et al. Lifestyle modifications to help prevent headache at a developmental age. *Front Neurol*. 2020;11:618375. DOI: 10.3389/fneur.2020.618375.
9. Orr SL. The evidence for the role of nutraceuticals in the management of pediatric migraine: A review. *Curr Pain Headache Rep*. 2018;22. DOI: 10.1007/s11916-018-0692-6.
10. AAN. Guidelines under Development. Available at: www.aan.com/practice/guidelines-under-development (accessed: 13 April 2026).
11. Ng QX, Venkatanarayanan N, Kumar L. A systematic review and meta-analysis of the efficacy of cognitive behavioral therapy for the management of pediatric migraine. *Headache*. 2017;57:349–62. DOI: 10.1111/head.13016.
12. Powers SW, Kashikar-Zuck SM, Allen JR, et al. Cognitive behavioral therapy plus amitriptyline for chronic migraine in children and adolescents. *JAMA*. 2013;310:2622. DOI: 10.1001/jama.2013.282533.
13. Stubberud A, Varkey E, McCrory DC, et al. Biofeedback as prophylaxis for pediatric migraine: A meta-analysis. *Pediatrics*. 2016;138:e20160675. DOI: 10.1542/peds.2016-0675.
14. Buse DC, Rabany L, Lin T, et al. Combining guided intervention of education and relaxation (GIER) with remote electrical neuromodulation (REN) in the acute treatment of migraine. *Pain Med*. 2022;23:1544–9. DOI: 10.1093/pm/pnac021.
15. Cocores AN, Smirnoff L, Greco G, et al. Update on neuromodulation for migraine and other primary headache disorders: Recent advances and new indications. *Curr Pain Headache Rep*. 2025;29. DOI: 10.1007/s11916-024-01314-7.
16. Oskoui M, Pringsheim T, Billinghurst L, et al. 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. *Neurology*. 2019;93:500–9. DOI: 10.1212/WNL.0000000000008105.
17. Orr SL. Headache in children and adolescents. *Continuum (Minneap Minn)*. 2024;30:438–72. DOI: 10.1212/CON.0000000000001414.
18. Shahrokhi M, Pur A, Shafaei-Bajestani N, Mashayekhi-Sardoo H. Levetiracetam for pediatric migraine prophylaxis: A narrative review. *Brain Dev*. 2025;47:104304. DOI: 10.1016/j.braindev.2024.104304.
19. Peng J, Liu L, Li Q, et al. Efficacy and safety of levetiracetam for migraine prophylaxis in children: A systematic review and meta-analysis. *Front Pharmacol*. 2024;15:1407897. DOI: 10.3389/fphar.2024.1407897.
20. Powers SW, Coffey CS, Chamberlin LA, et al. Trial of amitriptyline, topiramate, and placebo for pediatric migraine. *N Engl J Med*. 2017;376:115–24. DOI: 10.1056/NEJMoa1610384.
21. Aurora S, Dodick D, Turkel C, et al. OnabotulinumtoxinA for treatment of chronic migraine: Results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. *Cephalalgia*. 2010;30:793–803. DOI: 10.1177/0333102410364676.
22. Oskoui M, Pringsheim T, Holler-Managan Y, et al. Practice guideline update summary: Acute treatment of migraine in children and adolescents. *Neurology*. 2019;93:487–99. DOI: 10.1212/WNL.0000000000008095.
23. VanderPluym JH, Victorio MCC, Oakley CB, et al. Beyond the guidelines. *Neurology*. 2023;101:788–97. DOI: 10.1212/WNL.0000000000207677.
24. Edvinsson L, Haanes KA, Warfvinge K, Krause DN. CGRP as the target of new migraine therapies — Successful translation from bench to clinic. *Nat Rev Neurol*. 2018;14:338–50. DOI: 10.1038/s41582-018-0003-1.
25. Zhu G, Yan G, Luo Y, Luo J. Calcitonin gene-related peptide (cgrp) levels of children and adolescents with migraine: A systematic review and meta-analysis of observational studies. *Eur J Pain*. 2026;30:e70177. DOI: 10.1002/ejp.70177.
26. ICHD-3. 1.3 Chronic Migraine. Available at: https://ichd-3.org/1-migraine/1-3-chronic-migraine/ (accessed: 2 March 2026).
27. Goadsby PJ, Reuter U, Hallström Y, et al. A controlled trial of erenumab for episodic migraine. *N Engl J Med*. 2017;377:2123–32. DOI: 10.1056/NEJMoa1705848.
28. Yu S, Kim B-K, Wang H, et al. A phase 3, randomised, placebo-controlled study of erenumab for the prevention of chronic migraine in patients from Asia: The DRAGON study. *J Headache Pain*. 2022;23:146. DOI: 10.1186/s10194-022-01514-9.
29. Dodick DW, Ashina M, Brandes JL, et al. ARISE: A phase 3 randomized trial of erenumab for episodic migraine. *Cephalalgia*. 2018;38:1026–37. DOI: 10.1177/0333102418759786.
30. Goadsby PJ, Reuter U, Hallström Y, et al. One-year sustained efficacy of erenumab in episodic migraine: Results of the STRIVE study. *Neurology*. 2020;95:e469–79. DOI: 10.1212/WNL.0000000000010019.
31. Dodick DW, Silberstein SD, Bigal ME, et al. Effect of fremanezumab compared with placebo for prevention of episodic migraine: A randomized clinical trial. *JAMA*. 2018;319:1999–2008. DOI: 10.1001/jama.2018.4853.
32. Silberstein SD, Dodick DW, Bigal ME, et al. Fremanezumab for the preventive treatment of chronic migraine. *N Engl J Med*. 2017;377:2113–22. DOI: 10.1056/NEJMoa1709038.
33. Goadsby PJ, Silberstein SD, Yeung PP, et al. Long-term safety, tolerability, and efficacy of fremanezumab in migraine: A randomized study. *Neurology*. 2020;95:e2487–99. DOI: 10.1212/WNL.0000000000010600.
34. Camporeale A, Kudrow D, Sides R, et al. A phase 3, long-term, open-label safety study of galcanezumab in patients with migraine. *BMC Neurol*. 2018;18:188. DOI: 10.1186/s12883-018-1193-2.
35. Skljarevski V, Matharu M, Millen BA, et al. Efficacy and safety of galcanezumab for the prevention of episodic migraine: Results of the EVOLVE-2 Phase 3 randomized controlled clinical trial. *Cephalalgia*. 2018;38:1442–54. DOI: 10.1177/0333102418779543.
36. Stauffer VL, Dodick DW, Zhang Q, et al. Evaluation of galcanezumab for the prevention of episodic migraine: The EVOLVE-1 randomized clinical trial. *JAMA Neurol*. 2018;75:1080–8. DOI: 10.1001/jamaneurol.2018.1212.
37. Detke HC, Goadsby PJ, Wang S, et al. Galcanezumab in chronic migraine: The randomized, double-blind, placebo-controlled REGAIN study. *Neurology*. 2018;91:e2211–21. DOI: 10.1212/WNL.0000000000006640.
38. Lipton RB, Goadsby PJ, Smith J, et al. Efficacy and safety of eptinezumab in patients with chronic migraine: PROMISE-2. *Neurology*. 2020;94:e1365–77. DOI: 10.1212/WNL.0000000000009169.
39. Smith TR, Janelidze M, Chakhava G, et al. Eptinezumab for the prevention of episodic migraine: Sustained effect through 1 year of treatment in the PROMISE-1 study. *Clin Ther*. 2020;42:2254–65. DOI: 10.1016/j.clinthera.2020.11.007.
40. Ashina M, Saper J, Cady R, et al. Eptinezumab in episodic migraine: A randomized, double-blind, placebo-controlled study (PROMISE-1). *Cephalalgia*. 2020;40:241–54. DOI: 10.1177/0333102420905132.
41. Kudrow D, Cady RK, Allan B, et al. Long-term safety and tolerability of eptinezumab in patients with chronic migraine: A 2-year, open-label, phase 3 trial. *BMC Neurol*. 2021;21:126. DOI: 10.1186/s12883-021-02123-w.
42. Pozo-Rosich P, Ailani J, Ashina M, et al. Atogepant for the preventive treatment of chronic migraine (PROGRESS): A randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2023;402:775–85. DOI: 10.1016/S0140-6736(23)01049-8.
43. Ailani J, Lipton RB, Goadsby PJ, et al. Atogepant for the preventive treatment of migraine. *N Engl J Med*. 2021;385:695–706. DOI: 10.1056/NEJMoa2035908.
44. Ashina M, Tepper SJ, Reuter U, et al. Once-daily oral atogepant for the long-term preventive treatment of migraine: Findings from a multicenter, randomized, open-label, phase 3 trial. *Headache*. 2023;63:79–88. DOI: 10.1111/head.14439.
45. Croop R, Ailani J, Kudrow D, et al. Effects of rimegepant 75 mg on monthly migraine days: A 52-week, open-label extension study. *Neurology*. 2023;100:10–2. DOI: 10.1212/WNL.0000000000202051.
46. Croop R, Lipton RB, Kudrow D, et al. Oral rimegepant for preventive treatment of migraine: A phase 2/3, randomised, double-blind, placebo-controlled trial. *Lancet*. 2021;397:51–60. DOI: 10.1016/S0140-6736(20)32544-7.
47. Charles AC, Digre KB, Goadsby PJ, et al. Calcitonin gene-related peptide-targeting therapies are a first-line option for the prevention of migraine: An American Headache Society position statement update. *Headache*. 2024;64:333–41. DOI: 10.1111/head.14692.
48. Bandatmakur ASM, Dave P, Kerr M, et al. Effectiveness and tolerability of anti-calcitonin gene-related peptide therapy for migraine and other chronic headaches in adolescents and young adults: A retrospective study in the USA. *Brain Sci*. 2024;14:879. DOI: 10.3390/brainsci14090879.
49. US Food and Drug Administration. FDA Approves Drug for the Preventive Treatment of Episodic Migraine in Children Ages 6

Years and Older Who Weigh 45 kg or More. Available at: https://content.govdelivery.com/accounts/USFDA/bulletins/3eca033 (accessed: 04 February 2025).
50. Hershey AD, Szperka CL, Barbanti P, et al. Fremanezumab in children and adolescents with episodic migraine. *N Engl J Med*. 2026;394:243–52. DOI: 10.1056/NEJMoa2504546.
51. ClinicalTrials.gov. A Study to Test if Fremanezumab is Effective in Preventing Chronic Migraine in Participants 6 to 17 Years of Age. ClinicalTrials.gov identifier: NCT04464707. Available at: https://clinicaltrials.gov/study/NCT04464707 (accessed: 3 July 2026).
52. ClinicalTrials.gov. A Study to Test if Fremanezumab is Effective in Preventing Migraine in Children and Adolescents. ClinicalTrials.gov identifier: NCT04530110. Available at: https://clinicaltrials.gov/study/NCT04530110 (accessed: 3 July 2026).
53. ClinicalTrials.gov. Efficacy and Safety of Erenumab in Pediatric Participants With Episodic Migraine (OASIS(EM)). ClinicalTrials.gov identifier: NCT03836040. Available at: https://clinicaltrials.gov/study/NCT03836040 (accessed: 3 July 2026).
54. ClinicalTrials.gov. Efficacy and Safety of Erenumab in Pediatric Subjects With Chronic Migraine (OASIS(CM)). ClinicalTrials.gov identifier: NCT03832998. Available at: https://clinicaltrials.gov/study/NCT03832998 (accessed: 3 July 2026).
55. ClinicalTrials.gov. A Study of Galcanezumab (LY2951742) in Participants 12 to 17 Years of Age With Chronic Migraine (REBUILD-2). ClinicalTrials.gov identifier: NCT04616326. Available at: https://clinicaltrials.gov/study/NCT04616326 (accessed: 3 July 2026).
56. ClinicalTrials.gov. A Study of Galcanezumab (LY2951742) in Participants 6 to 17 Years of Age With Episodic Migraine (REBUILD-1). ClinicalTrials.gov identifier: NCT03432286. Available at: https://clinicaltrials.gov/study/NCT03432286 (accessed: 3 July 2026).
57. ClinicalTrials.gov. A Study of Eptinezumab in Pediatric Participants With Episodic Migraine (PROSPECT-1). ClinicalTrials.gov identifier: NCT05897320. Available at: https://clinicaltrials.gov/study/NCT05897320 (accessed: 3 July 2026).
58. ClinicalTrials.gov. A Study With Eptinezumab in Children and Adolescents (6 to 17 Years) With Chronic or Episodic Migraine (REJOIN). ClinicalTrials.gov identifier: NCT05164172. Available at: https://clinicaltrials.gov/study/NCT05164172 (accessed: 3 July 2026).
59. ClinicalTrials.gov. A Study With Eptinezumab in Adolescents (12-17 Years) With Chronic Migraine (PROSPECT-2). ClinicalTrials.gov identifier: NCT04965675. Available at: https://clinicaltrials.gov/study/NCT04965675 (accessed: 3 July 2026).
60. ClinicalTrials.gov. A Study of Oral Atogepant Tablets to Assess Adverse Events and Change in Disease Activity To Prevent Migraine in Participants Aged 12 to 17 Years. ClinicalTrials.gov identifier: NCT06810505. Available at: https://clinicaltrials.gov/study/NCT06810505 (accessed: 3 July 2026).
61. ClinicalTrials.gov. A Study to Assess the Adverse Events and Change in Disease Activity of Oral Atogepant Tablets in Pediatric Participants (6-17 Years of Age) With Episodic Migraine. ClinicalTrials.gov identifier: NCT05711394. Available at: https://clinicaltrials.gov/study/NCT05711394 (accessed: 3 July 2026).
62. ClinicalTrials.gov. Long-term Extension Study to Assess Adverse Events of Oral Atogepant Tablets in Pediatric Participants (6 to 17 Years of Age) With Migraine (Kaleidoscope). ClinicalTrials.gov identifier: NCT05707949 Available at: https://clinicaltrials.gov/study/NCT05707949 (accessed: 3 July 2026).
63. ClinicalTrials.gov. Long-term Safety Study of Rimegepant in Pediatric Subjects for the Acute Treatment of Migraine. ClinicalTrials.gov identifier: NCT04743141. Available at: https://clinicaltrials.gov/study/NCT04743141 (accessed: 3 July 2026).
64. ClinicalTrials.gov. Efficacy and Safety Study of Rimegepant for the Preventative Treatment of Migraine in Pediatric Subjects. ClinicalTrials.gov identifier: NCT05156398. Available at: https://clinicaltrials.gov/study/NCT05156398 (accessed: 3 July 2026).
65. ClinicalTrials.gov. A Study to Learn About the Study Medicine Called Rimegepant in Adolescents With Frequent Migraine. ClinicalTrials.gov identifier: NCT06616194. Available at: https://clinicaltrials.gov/study/NCT06616194 (accessed: 3 July 2026).
66. Szperka CL, VanderPluym J, Orr SL, et al. Recommendations on the use of anti-CGRP monoclonal antibodies in children and adolescents. *Headache*. 2018;58:1658–69. DOI: 10.1111/head.13414.
67. Russo AF, Kaiser EA. CGRP and migraine: real-world insights and future therapeutic directions. *Annu Rev Med*. 2026;77:415–32. DOI: 10.1146/annurev-med-050224-111631.
68. Smith AM, Schefter ZJ, Rogan H. Aligning with patients and families: Exploring youth and caregiver openness to pediatric headache interventions. *Children (Basel)*. 2022;9:1956. DOI: 10.3390/children9121956.
69. Nandyala AS, Tan K, Africk B, et al. Socioeconomic factors associated with migraine medication prescription at a tertiary headache center. *Neur Clin Pract*. 2025;15. DOI: 10.1212/CPJ.0000000000200517.
70. Na J-H, Jeon H, Shim J-E, et al. Effectiveness and safety of CGRP-targeted therapies combined with lifestyle modifications for chronic migraine in Korean pediatric patients: A retrospective study. *Brain Sci*. 2025;15:493. DOI: 10.3390/brainsci15050493.
71. Pellesi L, Garcia-Azorin D, Rubio-Beltrán E, et al. Combining treatments for migraine prophylaxis: The state-of-the-art. *J Headache Pain*. 2024;25. DOI: 10.1186/s10194-024-01925-w.