Review article

The effect of prophylactic drugs in pediatric and adolescent migraine compared to placebo

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Efecto de fármacos profilácticos en migraña infantil y adolescente comparado con placebo

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Abstract
Migraine is a common neurological disorder in children and adolescents, with a prevalence of 11%. It causes functional impairment and a reduced quality of life, and may lead to episodes of chronic migraine; therefore, pharmacological prophylaxis is a fundamental part of a long-term treatment plan aimed at reducing the recurrence and intensity of migraine episodes. The objective of this review article is to determine, in pediatric and adolescent patients with migraine, the effect of a pharmacological prophylactic approach compared to placebo on the recurrence of migraine episodes. To this end, a literature review was conducted in the following databases: ScienceDirect, PubMed, and SciELO; open-access articles containing the MeSH terms "migraine," "prophylaxis," and "pediatric population" were included, across the categories of review articles, original articles, and meta-analyses in English and Spanish, published between 2019 and 2025. It is concluded that migraine prophylaxis in the pediatric population is in the early stages of research, with limitations in the evaluated studies that make it difficult to achieve statistical significance for all the treatment options described; therefore, more evidence is needed to reach a consensus on the management of this condition.

Keywords
Migraine Disorders, Child, Adolescent.

Resumen
La migraña es un trastorno neurológico común en la población pediátrica y adolescente con una prevalencia de 11 %, provoca un deterioro funcional en la calidad de vida y la posibilidad de episodios de migraña crónica, por lo que su profilaxis farmacológica es una parte fundamental para un plan de tratamiento a largo plazo, cuyo objetivo es disminuir la recurrencia e intensidad de los episodios migrañosos. El objetivo de esta revisión narrativa es determinar, en pacientes pediátricos y adolescentes con migraña, el efecto del abordaje farmacológico profiláctico en comparación al placebo sobre la recurrencia de episodios de migraña. Para esto se realizó una revisión bibliográfica en las bases de datos: ScienceDirect, Pubmed y SciELO; se incluyeron artículos de libre acceso con términos MeSH de migraña, profilaxis y población pediátrica, en las categorías: artículos de revisión, originales y metaanálisis en inglés y español, publicados entre 2019 y 2025. Se concluye que la profilaxis para migraña en población pediátrica se encuentra en fases tempranas de investigación, con limitaciones en los estudios evaluados que dificultan alcanzar la significancia estadística en todas las opciones de tratamiento descritas, donde amerita una mayor cantidad de evidencia para poder formular un consenso del manejo de esta condición.

Palabras clave
Trastornos migrañosos, Niños, Adolescentes.

Introduction

Headaches are classified as primary or secondary. Among the primary causes are primarily migraines, a common neurological disorder in children, with an estimated overall prevalence of 11 %. Prevalence increases with age, ranging from 3 % to 8 % in children aged three to seven years, up to 23 % in adolescents aged 11 to 15 years. Males have a higher prevalence before puberty; however, the incidence and prevalence increase more rapidly with age in girls, so after puberty, the prevalence is higher in females.[1,2]

Seven million children and adolescents worldwide are affected by migraine, which causes functional impairment in multiple areas of their daily lives. Migraines represent a major cause of social disability and are among the top five health problems in childhood; up to 8 % of children and adolescents experience migraines over a period of at least three months at some point in their lives.[3,4]

Migraine in the pediatric population has a negative impact on quality of life and academic performance and is also associated with future psychological disorders such as depression and anxiety disorders. Approximately half of the pediatric population continues to suffer from migraines into adulthood.[5,6]

Pharmacological prophylaxis for migraine in the pediatric population is essential for establishing a long-term treatment plan and aims to reduce the recurrence and intensity of migraine episodes. Topiramate is the only drug approved by the Food and Drug Administration (FDA) for prophylaxis in the pediatric population, with 77.3 % of patients showing a good response to the medication, resulting in a reduction in the average duration of migraine episodes from 2.28 ± 1.55 to 0.94 ± 0.35 hours, as well as a reduction in the intensity of migraine attacks.[7-10]

Prophylaxis for the pediatric management of migraine is in the early stages of research, with options such as pregabalin, melatonin, magnesium, and vitamin D3 currently being studied for their ability to reduce the frequency of migraine episodes. Similarly, propranolol, cinnarizine, magnesium, pregabalin, valproate, and levetiracetam, when compared with placebo, have been shown to reduce headache intensity.[1,11-15]

A review article of the literature was conducted following the recommendations of the Scale for the Assessment of Narrative Review Articles (SANRA). A literature search was conducted in the PubMed, ScienceDirect, and SciELO databases. The MeSH terms "Migraine" and "Pediatrics" were used, combined using the Boolean operator AND; additionally, the terms "prophylaxis," "preventive measures," and "placebo" were included using the OR operator. Original articles, reviews, and meta-analyses published in English or Spanish between 2019 and 2025 were included. The objective of the review was to identify recent advances in the pharmacological prophylaxis of pediatric migraine, evaluate its efficacy in reducing the recurrence of episodes compared with placebo, and synthesize the available evidence regarding its efficacy and safety.[16,17]

Discussion

Migraine and the basics of its pharmacological management for pediatric and adolescent patients

According to the International Headache Society's third edition, headaches are classified as primary or secondary; primary headaches include migraine. Migraine is divided into two main types: migraines with aura and migraines without aura. The former are characterized by at least five headache episodes lasting from four to 72 hours, with at least two of the following characteristics: unilateral, throbbing, moderate to severe in intensity, or worsening with or preventing daily activities. Additionally, they are accompanied by at least one of the following: nausea and/or vomiting, or photophobia and phonophobia.[18]

Migraines with aura meet the aforementioned criteria and are accompanied by one or more reversible aura symptoms with at least three of the following characteristics: gradual onset of aura symptoms, two or more aura symptoms, each aura symptom lasts from five to 60 minutes, at least one aura symptom is unilateral, at least one aura symptom is positive, and the aura occurs within 60 minutes of a headache. Based on their duration, they can be classified as chronic migraines, which are those that occur on at least eight days per month for more than three months.[18]

Migraine is considered a debilitating neurological disorder, characterized by functional impairment secondary to a headache episode, along with associated symptoms such as nausea, photophobia, and phonophobia, among others; this impairs individuals' quality of life. The goal of acute treatment, as defined by the American Headache Society, is primarily to provide rapid and sustained relief from the headache and associated symptoms.[19,20]

The acute management of migraines in children and adolescents relies on medications commonly used in adults: the triptan class, nonsteroidal anti-inflammatory drugs, acetaminophen, selective serotonin reuptake inhibitors, among others. These are not always effective and may cause long-term side effects.[21,22]

In cases of chronic migraine, many patients rely solely on treatment for acute episodes, which can lead to further deterioration of health and medication-overuse headaches. The American Headache Society recommends that, for chronic migraine, preventive treatments such as lifestyle changes, focused on SMART (sleep, meals, activity, relaxation, triggers),

be used to reduce the frequency and severity of episodes, as well as to improve function, quality of life, and reduce disability. Approved preventive medications include: sodium valproate, flunarizine, topiramate, propranolol, and timolol.[23-25]

Preventive treatment is primarily indicated for those suffering from chronic migraine and for individuals with frequent, severe, or prolonged episodic migraines. Its main objective is to achieve a reduction of at least 50 % in the average duration of migraine episodes and at least 30 % in chronic migraines.[26,27]

Effect of pharmacological prophylactic measures on migraine episodes in the pediatric and adolescent population

Among the pharmacological options for migraine prophylaxis is magnesium, a micronutrient that influences the regulation of glutamatergic excitation at N-methyl-D-aspartate (NMDA) receptors. Evidence shows that in a state of hypomagnesemia, the neuronal cells involved in pain transmission become hyperexcited; furthermore, this leads to widespread cortical depression, which increases the incidence of migraine attacks. The study by Domínguez *et al.* showed that the administration of 9 mg/kg of oral magnesium in a pediatric population resulted in a decrease in the frequency and intensity of migraine attacks.[15]

Topiramate, in addition to its anticonvulsant activity, has recently been shown to be effective in the prophylaxis of migraine attacks. Its specific mechanism is unknown; however, the most widely accepted theory is that it reduces the release of excitatory neurotransmitters, thereby decreasing the neuronal excitability involved in pain transmission.[8] Its efficacy has recently been demonstrated in the pediatric population; in an experimental study by Surani MK *et al.*, conducted in Pakistan with children aged from five to 15 years, a significant reduction in the frequency, intensity, and duration of migraine attacks was observed.[28]

Among botulinum toxins, OnabotulinumtoxinA has been shown to be effective due to its ability to block the release of acetylcholine, which in turn inhibits the release of substance P, glutamate, and calcitonin gene-related peptide. OnabotulinumtoxinA was approved by the FDA in 2010[27] for the treatment of migraine in adults, but not in children. In the studies by Akbar *et al.*, (a retrospective review) and Shah *et al.*, (a double-blind experimental study), a significant decrease in the frequency ($p = 0.038$) and intensity of migraine attacks ($p = 0.047$) was reported; Additionally, they described improved mood and better concentration in 50 % of the population treated with OnabotulinumtoxinA.[30,31]

Among calcium channel blockers, flunarizine and cinnarizine are medications used to prevent migraine attacks. The guidelines of the American Academy of Neurology and the American Headache Society mention cinnarizine as a prophylactic option that has been reported to reduce the severity of migraine attacks as well as decrease their frequency by 50 %,[32] Furthermore, in the randomized trial by Vaswani *et al.*, flunarizine was found to be as effective as propranolol in treating migraine attacks in the pediatric population, resulting in a 50 % reduction in the number of days with migraine attacks.[33]

Amitriptyline, a tricyclic antidepressant, is a prophylactic option for migraine attacks. Its anti-migraine mechanism is complex; the drug inhibits the neurotransmitter 5-hydroxytryptamine in the synaptic cleft of pain pathways.[34] In the clinical trial by Olfat *et al.*, a randomized, double-blind comparison was conducted between amitriptyline and cinnarizine, demonstrating that both are effective and safe for migraine prophylaxis, with no significant differences in the outcomes between the two medications.[16]

Propranolol is a beta-blocker whose antimigraine mechanisms are nonspecific; some proposed mechanisms include inhibition of cortical spreading depression or trigeminovascular nociception in the ventroposteromedial nucleus of the thalamus.[35] In the clinical trial by Vaswani *et al.*, propranolol and flunarizine were compared in a pediatric population; similarly, both demonstrated satisfactory results as monotherapy.[33] Likewise, in the clinical trial by Fayyazi *et al.*, propranolol, levetiracetam, and sodium valproate were evaluated for their prophylactic effectiveness; it was reported that propranolol is effective for preventing migraines and reducing their intensity, with effects comparable to those of sodium valproate, and it also yielded better results than the group treated with levetiracetam.[36]

Among anticonvulsants, the only one approved in the United States as a prophylactic treatment for migraine in adults is sodium valproate. The proposed mechanism of action for this medication is the modulation of gamma-aminobutyric acid (GABA) to inhibit nociceptive neurotransmission and reduce neurogenic inflammation.[37]

It has recently been compared with other prophylactic medications in pediatric patients; in the clinical trial by Amanat

et al., the intervention was compared with cinnarizine in terms of reducing the frequency of migraine attacks. From the start of treatment, the mean difference was −8.3 episodes (95 % CI: −9.3 to −7.2) in the intervention group and −8.0 episodes (95 % CI: −9.3 to −6.6) in the cinnarizine group.[5] In the clinical trial by Khani *et al.*, the effects of sodium valproate and magnesium were compared, and the results showed greater effectiveness in reducing the frequency and intensity of attacks with sodium valproate compared to the group treated with magnesium monotherapy; however, an even more satisfactory result was obtained with combination therapy.[38] Similarly, the clinical trial by Bidabadi *et al.* demonstrated the synergistic effect of probiotics in patients receiving sodium valproate, resulting in a reduced need for monthly analgesics.[39]

Among the medications currently under investigation for pediatric use are monoclonal antibodies, the most extensively studied of which are eptinezumab and erenumab. Their mechanism of action involves inhibiting the calcitonin gene, which encodes a peptide implicated in migraine.[40] However, these drugs have been approved only for use in adults; eptinezumab is currently in Phase three trials, and erenumab is in Phase one trials in the pediatric population.[41-42] In the clinical trial by Greene *et al.*[44] involving adolescents, the effectiveness of monoclonal antibodies, primarily erenumab, was established at 86-87 %, resulting in symptomatic improvement in 71.5 % of the patients included in the study after 2.7 months of monotherapy.

Among other medications, for which fewer studies exist, are probiotics, which-in addition to their synergistic effect with sodium valproate-also demonstrated, in the clinical trial by Martami *et al.*, a reduction in the frequency, duration, and monthly use of rescue analgesics.[45] Another supplement under study is alpha-lipoic acid: in the clinical trial by Puliappadamb *et al.*, improvement was reported in patients treated with flunarizine in combination with alpha-lipoic acid, compared to those in the group receiving flunarizine monotherapy, who showed a lower degree of symptomatic improvement.[46]

Effect of pharmacological prophylactic approaches to reduce migraine-induced disability versus placebo in the pediatric and adolescent population

Chronic migraine has been identified by the Global Burden of Disease 2021 study as the neurological disorder with the greatest impact on quality of life in the pediatric and adolescent population, causing academic disability due to missed school days, economic disability due to the ongoing cost of rescue medications during attacks, and psychological disability due to the future development of depressive and anxiety disorders. Several prophylactic treatments have been proposed to address these disabilities.[47]

Magnesium nutritional supplementation

In the randomized clinical trial conducted by Khani S, *et al.*, magnesium supplementation was shown, using the standardized Migraine Disability Assessment (MIDAS) tool, to be effective; furthermore, in this randomized clinical trial conducted by Khani *et al.*, the intervention under evaluation produced a statistically significant reduction in migraine-related disability, as measured by the Migraine Disability Assessment (MIDAS), with a decrease from 22.13 ± 1.88 points before the intervention to 18.81 ± 1.76 points after the intervention ($p < 0.001$). However, the magnitude of the reduction was greater in patients treated with sodium valproate, whose MIDAS scores decreased from 21.74 ± 4.44 to 17.11 ± 4.06, and was even greater in the group that received the combination of both interventions, in which the scores decreased from 21.68 ± 3.72 to 16.11 ± 3.87 ($p < 0.001$). In addition, a statistically significant difference in post-treatment disability was observed between the group receiving sodium valproate and the group treated with the combination of both interventions ($p = 0.023$).[38] However, no equivalent studies conducted in a pediatric population over the past five years were identified.

Topiramate

The Childhood and Adolescent Migraine Prevention Trial (CHAMP), conducted by Powers *et al.*, in 2016, was a clinical trial involving 361 patients randomly assigned to receive topiramate, amitriptyline, or placebo over a two-year period. Migraine-induced disability was assessed based on the reduction in the recurrence of disabling episodes; however, the results were not statistically significant when comparing amitriptyline to placebo on this measure (Odds Ratio 0.71, 98.3 % CI, 0.34 to 1.48; $p = 0.26$) and topiramate versus placebo (Odds Ratio 0.81, 98.3 % CI, 0.39 to 1.68; $p = 0.48$), leading to the initial conclusion that these medications were not as effective in this pediatric population as they are in adults.

Additionally, 12 severe adverse events were reported during the study, of which five were determined to be treatment-related: three cases of mood changes in the amitriptyline group, one case of syncope in the same group, and one case of a suicide attempt in the topiramate group.[48] Treatment adherence should be noted as a limitation of the CHAMP study; another limitation was the failure to use a standardized disability assessment tool such as the MIDAS.

In 2021, Reidy *et al.* conducted a secondary analysis of data from CHAMP study participants and observed high subjective treatment adherence during the six-month follow-up period, with self-reported values averaging over 90 %. However, objective assessment using serum concentrations showed a decrease in the proportion of participants with detectable drug levels, from 84 % to 76 %, between two measurements taken three months apart. This reduction was statistically significant ($p < 0.001$) and demonstrated a discrepancy between self-reported adherence and adherence estimated using pharmacological biomarkers during the CHAMP study.[49]

Given the limitations previously identified in the CHAMP study, Reidy *et al.* conducted a new analysis of their data in 2022 using additional statistical methods. The authors identified a significant downward trend during both the baseline phase (–0.35) and the active treatment phase (–0.132), with overall statistical significance ($p < 0.001$). However, no significant differences were observed between the treatment groups. Consequently, the authors concluded that, although a progressive reduction in the assessed outcome was evident over time, this improvement could not be differentially attributed to any of the interventions studied; they therefore recommended further research to clarify their therapeutic effect.[50]

Subsequently, in 2021, Powers *et al.* conducted a prospective study, a three-year follow-up of the original CHAMP study involving 153 patients who had completed that study, which showed that the average perceived disability score using the PedMIDAS (Pediatric MIDAS) of 40.9 at the start of the CHAMP study and 12.3 at the end of the three-year follow-up, which was not significantly associated with the use of amitriptyline ($p = 0.12$) or topiramate ($p = 0.24$); furthermore, only one patient remained on preventive treatment during the follow-up period.[51]

In this review, limited to evidence published over the past five years, no other studies were identified that specifically evaluated the effect of topiramate on migraine-related disability.

OnabotulinumtoxinA

OnabotulinumtoxinA (OBTA) was the subject of a study in a pediatric population in the clinical trial conducted by Shah *et al.*, which compared a group receiving OBTA with a group receiving a placebo, evaluating parameters that included PedMIDAS, and a statistically significant reduction in disability caused by migraine episodes was reported (modified PedMIDAS three (2-4) vs. four (4-4), $p < 0.047$); however, it should be noted that this study has a limitation: only 15 participants were recruited for the study.[30]

Another clinical trial, conducted by Winner *et al.*, evaluated three groups comprising a total of 125 patients: patients treated with a 155 IU dose, a 74 IU dose, or a placebo. The results showed a decrease in disability as measured by PedMIDAS across all three groups (Average change in PedMIDAS scores compared to baseline for OBTA 155U, OBTA 74U, and placebo, respectively: -19.5, -36.1, and -32.6); however, this difference was not statistically significant ($p=0.114$); the authors suggest that a study with a larger sample size will be necessary to confidently demonstrate the treatment's efficacy.[52]

Over the past five years, no other articles were found that studied OBTA for use in cases of chronic migraine in the pediatric population; based on the current literature, there is insufficient statistical significance to approve its use at this time, and further studies are needed.

Calcium channel blockers

These include flunarizine and cinnarizine. The clinical trial by Vaswani *et al.* demonstrated a reduction in perceived disability among patients, as measured by the standardized PedMIDAS scale, in both the group treated with propranolol and the group treated with flunarizine; however, it should be noted that this study has statistical limitations, such as a total sample size of 40 patients, and did not achieve statistical significance for the reduction in PedMIDAS scores between groups ($p = 0.924$); furthermore, although an average reduction in PedMIDAS of 8.2 is reported, no mention is made of whether this is statistically significant.[33]

In the clinical trial conducted by Olfat *et al.*, the efficacy of cinnarizine was compared with that of amitriptyline, and migraine-related disability was assessed using the Pediatric Migraine Disability Assessment (PedMIDAS) scale. In the cinnarizine-treated group, the average PedMIDAS score decreased from 41.52 ±

38.0 at the start of the study to 25.0 ± 24.6 at the end of treatment, representing a statistically significant reduction from baseline (p = 0.021). However, when comparing the results with the amitriptyline-treated group, which showed a decrease from 40.37 ± 30.5 to 24.30 ± 23.0 points, no statistically significant differences were observed between the two treatments (p = 0.31).[16]

In the clinical trial conducted by Amanat *et al.*, the efficacy of cinnarizine, sodium valproate, and placebo was compared for migraine prophylaxis. Compared with placebo, cinnarizine produced a statistically significant reduction in both the frequency of migraine episodes (mean difference: −3.4; 95 % CI: −4.9 to −1.9; p < 0.001) and their intensity (mean difference: −1.5; 95 % CI: −2.4 to −0.6; p < 0.001). However, when compared with sodium valproate, no statistically significant differences were observed in the frequency of episodes (mean difference: −0.3; 95 % CI: −1.8 to 1.1; p = 0.854) or in their intensity (mean difference: 0.1; 95 % CI: −0.8 to 1.0; p = 0.960). These findings suggest comparable efficacy between cinnarizine and sodium valproate for both outcomes. However, the authors noted as a limitation that the frequency and intensity of attacks were recorded subjectively by parents, without using a standardized scale to assess migraine-related disability, such as the PedMIDAS.[5]

No other studies published during the five-year period analyzed were identified that evaluated the use of calcium channel blockers for migraine prophylaxis.

Tricyclic antidepressants

Regarding amitriptyline, the clinical trial conducted by Olfat *et al.*, showed a statistically significant reduction in migraine-related disability, as assessed by the PedMIDAS scale. In the amitriptyline-treated group, the mean score decreased from 40.37 ± 30.5 at the start of the study to 24.30 ± 23.0 at the end of treatment (p = 0.028). However, when comparing these results with those obtained in the cinnarizine-treated group-whose PedMIDAS scores decreased from 41.52 ± 38.0 to 25.0 ± 24.6 no statistically significant differences were observed between the two treatments (p = 0.31).[16]

In the clinical trial conducted by Yaghini *et al.*, the efficacy of amitriptyline was compared with that of coenzyme Q10, the latter being associated with a lower frequency of adverse effects. After three months of treatment, both groups showed statistically significant reductions from baseline in the frequency, duration, and intensity of migraine episodes (p < 0.001 for all parameters). In the group treated with coenzyme Q10, the frequency decreased from 8.75 ± 4.80 to 2.47 ± 2.31 episodes; the duration, from 4.89 ± 3.28 to 2.14 ± 1.94; and the intensity, from 6.61 ± 1.57 to 3.31 ± 2.40. When comparing the two treatments at three months, no statistically significant differences were observed in the frequency of episodes (amitriptyline: 2.28 ± 3.31; p = 0.228), their duration (1.85 ± 7.93; p = 0.831), or their intensity (2.78 ± 2.13; p = 0.244). However, at the one-month mark, amitriptyline showed a significantly greater reduction than coenzyme Q10 in all three outcomes evaluated: frequency (2.53 ± 1.75 vs. 8.00 ± 15.98; p < 0.001), duration (1.21 ± 1.92 vs. 3.67 ± 2.10; p < 0.001), and intensity (4.58 ± 1.70 vs. 5.36 ± 1.22; p = 0.025). These findings suggest a faster onset of action with amitriptyline, although at three months both interventions showed comparable efficacy in the evaluated parameters.[53]

The two studies mentioned above suggest that amitriptyline is significantly effective and carries a risk of adverse effects; however, recent articles have not identified a significantly superior alternative to its use.

To address the question regarding the effect of these medications on reducing disability, the findings from studies conducted over the past five years are summarized in Table 1.

Conclusion

Recent evidence on the prophylactic treatment of chronic migraine in the pediatric population remains limited and heterogeneous. Unlike what is observed in adults, significant gaps in knowledge persist, despite the impact of migraine on school functioning, quality of life, and the subsequent risk of affective and anxiety disorders. In this review, some interventions, such as magnesium sulfate, lacked sufficient recent pediatric evidence, while onabotulinumtoxinA and flunarizine showed potentially favorable results, although these were limited by a lack of statistical significance, small sample sizes, or other methodological limitations.

Among the pharmacological and complementary interventions evaluated, topiramate, amitriptyline, cinnarizine, coenzyme Q10, propranolol, and sodium valproate demonstrated statistically significant prophylactic effects on certain outcomes, primarily regarding the frequency, intensity, or duration of attacks and, in some studies, on migraine-related disability. However, the available evidence does not consistently

support the superiority of one intervention over the others, due to heterogeneity in study designs, comparators, outcomes, follow-up periods, and assessment methods.

Therapies targeting specific pathways in the pathophysiology of migraine, including monoclonal antibodies, represent an emerging strategy whose role in the pediatric population still requires further clarification. Overall, the findings of this review highlight the need for larger pediatric clinical trials with greater statistical power, featuring rigorous methodological designs, sufficient follow-up, and the systematic use of validated instruments, such as the PedMIDAS scale. Generating higher-quality comparative evidence will be essential for establishing more consistent recommendations, tailoring the selection of prophylactic treatment, and moving toward an evidence-based consensus for the management of migraine in children and adolescents.

Table 1. Summary of evidence on pharmacological medications used for prophylactic treatment and their effect on reducing disability.

Medicine	Compared to	Disability Reduction	Evaluated with	Limitations
Magnesium (in adults)	Valproic acid	Reduction, but less than valproic acid (p <0.001)	MIDAS	No equivalent pediatric studies were found
Magnesium + valproic acid	Valproic acid	Reduction, superior to valproic acid alone (p <0.001)	MIDAS + need for rescue medication	No equivalent pediatric studies were found
Topiramate	Pre-treatment baseline values	Significant reduction (p <0.001)	Incidence of disabling episodes	Adherence to treatment is doubtful No standardized scale was used
	Placebo	Reduction, but not greater than placebo in initial study (p = 0.48)	Incidence of disabling episodes	Adherence to treatment is doubtful No standardized scale was used
		Reduction, no greater than placebo in 3-year follow-up (p = 0.24)	PedMIDAS	Only 1 patient remained adherent to treatment after the original study
Amitriptilina	treatment baseline values	Significant reduction (p <0.001)	Incidence of disabling episodes	Uncertain treatment adherence; no standardized scale was used
		Significant reduction (p = 0.028)	PedMIDAS	Only 1 patient remained adherent to treatment after the original study
	Placebo	Reduction, but not greater than placebo in initial study (p = 0.26)	Incidence of disabling episodes	Adherence to treatment is doubtful No standardized scale was used
		Reduction, no greater than placebo in 3-year follow-up (p = 0.12)	PedMIDAS	Only 1 patient remained adherent to treatment after the original study
	Coenzyme Q10	Greater reduction in coenzyme at 1 month of treatment (p <0.001), with no significant difference at three months	Frequency, duration and intensity of migraine episodes	Yaghini, *et al*., does not use a standardized scale
OBTA	Placebo	Significant reduction (p< 0.47)	PedMIDAS	Shah, *et al*., total population of 15 patients
		Reduction, not significant (p = 0.114)	PedMIDAS	Winner, et al , population of 125 patients
Flunarizine	Pre-treatment baseline values	Reduction of 8.2 points on average (no mention is made about significance)	PedMIDAS	No mention is made of statistical significance Population of 40 patients
	Propranolol	Reduction, no greater and no less than propranolol (p= 0.924)	PedMIDAS	Population of 40 patients
Cinnarizine	Pre-treatment baseline values	Significant reduction (p = 0.021)	PedMIDAS	Olfat, *et al*., is not compared to placebo in this study.
	Amitriptyline	Reduction, not different from amitriptyline (p = 0.31)	PedMIDAS	Olfat, *et al*., is not compared to placebo in this study
	Placebo	Reduction in frequency (p > 0.001) and intensity (p < 0.001)	Frequency and intensity of disabling episodes	Amanat, *et al*., do not use a standardized disability scale
	Sodium valproate	Reduction, not significantly different (p = 0.854)	Frequency and intensity of disabling episodes	Amanat, *et al*., does not use a standardized disability scale

Source: Author's own work. Summary of evidence on pharmacological medications used for the prophylactic management of migraine in the pediatric population, including comparator data, the presence of a reduction in disability, the significance of this reduction, and the scales or parameters used to assess disability. Also included are limitations of the studies providing these results. **MIDAS:** Migraine Disability Assessment; **PedMIDAS:** Pediatric MIDAS; **OBTA:** OnabotulinumtoxinA.

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References

1. Kohandel Gargari O, Aghajanian S, Togha M, Mohammadifard F, Abyaneh R, Mobader Sani S, *et al.* Preventive Medications in Pediatric Migraine: A Network Meta-Analysis. JAMA Netw Open. 2024;7(10):e2438666. DOI: 10.1001/jamanetworkopen.2024.38666
2. Locher C, Kossowsky J, Koechlin H, Lam TL, Barthel J, Berde CB, *et al.* Efficacy, Safety, and Acceptability of Pharmacologic Treatments for Pediatric Migraine Prophylaxis: A Systematic Review and Network Meta-analysis. JAMA Pediatr. 1 de 2020;174(4):341-349. DOI: 10.1001/jamapediatrics.2019.5856
3. Onofri A, Necozione S, Tozzi E. Complementary and alternative medicine (CAM) in headache of children and adolescents: open-label Italian study. Clin Ter. 2020;171(5):e393-e398. DOI: 10.7417/CT.2020.2246
4. Gibler R, Peugh J, Coffey C, Chamberlin L, Ecklund D, Klingner E, *et al.* Impact of preventive pill-based treatment on migraine days: A secondary outcome study of the Childhood and Adolescent Migraine Prevention (CHAMP) trial and a comparison of self-report to nosology-derived assessments. Headache. 2023;63(6):805-812. DOI: 10.1111/head.14474
5. Amanat M, Togha M, Agah E, Ramezani M, Tavasoli A, Azizi Malamiri R, *et al.* Cinnarizine and sodium valproate as the preventive agents of pediatric migraine: A randomized double-blind placebo-controlled trial. Cephalalgia Int J Headache. 2020;40(7):665-674. DOI: 10.1177/0333102419888485
6. Ford J, Stauffer V, McAllister P, Akkala S, Sexson M, Ayer DW, *et al.* Functional impairment and disability among patients with migraine: evaluation of galcanezumab in a long-term, open-label study. Qual Life Res Int J Qual Life Asp Treat Care Rehabil. 2021;30(2):455-464. DOI: 10.1007/s11136-020-02632-0
7. Nwaobi SE, Kamins J. Implications of 3-Year Follow-up Data From the Childhood and Adolescent Migraine Prevention Medication Trial. JAMA Network Open. 2021;4(7):e2114788. DOI: 10.1001/jamanetworkopen.2021.14788
8. Hu C, Zhang Y, Tan G. Advances in topiramate as prophylactic treatment for migraine. Brain Behav. 20e21;11(10):e2290. DOI: 10.1002/brb3.2290
9. Surani MK, Yousuf M, Anjum N, Khan S, Hasan G, Hussain S. TOPIRAMATE FOR MIGRAINE PROPHYLAXIS AMONG CHILDREN AGED 5 TO 15 YEARS. Journal of Ayub Medical College Abbottabad. 2021;33(3):480-3. Available at: https://pubmed.ncbi.nlm.nih.gov/34487661/
10. U.S. Food and Drug Adminstration. TOPAMAX (Topiramate) Medication Guide. FDA. 2026. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2026/020505s068lbl.pdf#page=55
11. Keerthana D, Mishra D, Chauhan MK, Juneja M. Effect of Propranolol Prophylaxis on Headache Frequency in Children with Migraine Without Aura: A Randomized, Double-Blind, Placebo-Controlled Trial. Indian J Pediatr. 2023;90(9):880-885. DOI: 10.1007/s12098-022-04279-w
12. Das R, Qubty W. Retrospective Observational Study on Riboflavin Prophylaxis in Child and Adolescent Migraine. Pediatr Neurol. 2021;114:5-8. DOI: 10.1016/j.pediatrneurol.2020.09.009
13. Rettig E, Ergun G, Warfield J, Slater S, LeCates S, Kabbouche MA, *et al.* Predictors of Improvement in Pediatric Chronic Migraine: Results from the Cognitive-Behavioral Therapy and Amitriptyline Trial. J Clin Psychol Med Settings. 2022;29(1):113-119. DOI: 10.1007/s10880-021-09782-4
14. Gelfand A, Allen I, Grimes B, Irwin S, Qubty W, Greene K, *et al.* Melatonin for migraine prevention in children and adolescents: A randomized, double-blind, placebo-controlled trial after single-blind placebo lead-in. Headache. 2023;63(9):1314-1326. DOI: 10.1111/head.14600
15. Domínguez L, Veronese N, Sabico S, Al-Daghri NM, Barbagallo M. Magnesium and Migraine. Nutrients. 2025;17(4):725. DOI: 10.3390/nu17040725
16. Olfat M, Hosseinpour S, Masoumi S, Gogia Rastogi R, Vance Hastriter E, Lewis KS, *et al.* A comparative study on prophylactic efficacy of cinnarizine and amitriptyline in childhood migraine: a randomized double-blind clinical trial. Cephalalgia. 2024;44(4). DOI: 10.1177/03331024241230963

17. Nieswand V, Richter M, Gossrau G. Epidemiology of Headache in Children and Adolescents-Another Type of Pandemia. Curr Pain Headache Rep. 2020;24(10):62. DOI: 10.1007/s11916-020-00892-6
18. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018;38(1):1-211. DOI: 10.1177/0333102417738202
19. Tepper SJ, Vasudeva R, Krege J, Rathmann S, Doty E, Vargas BB, *et al.* Evaluation of 2-Hour Post-Dose Efficacy of Lasmiditan for the Acute Treatment of Difficult-to-Treat Migraine Attacks. Headache. 2020;60(8):1601-1615. DOI: 10.1111/head.13897
20. Tepper S, Albrecht D, Ailani J, Kirby L, Strom S, Rapoport AM. Long-Term (12-Month) Safety and Tolerability of STS101 (Dihydroergotamine Nasal Powder) in the Acute Treatment of Migraine: Data from the Phase 3 Open-Label ASCEND Study. CNS Drugs. 2024;38(12):1017-1027. DOI: 10.1007/s40263-024-01118-8
21. Tsai M, Nery ESM, Kerr L, Khanna R, Komori M, Dennehy EB, *et al.* Pharmacokinetics, Safety, and Tolerability of Lasmiditan in Pediatric Patients with Migraine. Clin Pharmacokinet. 2021;60(6):819-828. DOI: 10.1007/s40262-020-00966-z
22. Gelfand A, Ross AC, Irwin S, Greene K, Qubty WF, Allen I. Melatonin for Acute Treatment of Migraine in Children and Adolescents: A Pilot Randomized Trial. Headache. 2020;60(8):1712-1721. DOI: 10.1111/head.13934
23. Diener H, Day K, Lipsius S, Aurora S, Hindiyeh N, Detke H. Shift from chronic to episodic migraine frequency in a long-term phase 3 study of galcanezumab. J Headache Pain. 2025;26(1):26. DOI: 10.1186/s10194-025-01956-x
24. Ailani J, Lipton B, James P, Guo H, Goadsby M, *et al.* Atogepant for the Preventive Treatment of Migraine. N Engl J Med. 2021;385(8):695-706. DOI: 10.1056/NEJMoa2035908
25. Lipton R, Gandhi P, Tassorelli C, Reuter U, Harriott AM, Holle-Lee D, *et al.* Early Improvements With Atogepant for the Preventive Treatment of Migraine: Results From 3 Randomized Phase 3 Trials. Neurology. 2025;104(2):e210212. DOI: 10.1212/WNL.0000000000210212
26. Cohen-Barak O, Radivojevic A, Jones A, Fiedler-Kelly J, Gillespie M, Brennan M, *et al.* Dose selection for fremanezumab (AJOVY) phase 3 pediatric migraine studies using pharmacokinetic data from a pediatric phase 1 study and a population pharmacokinetic modeling and simulation approach. Cephalalgia Int J Headache. 2021;41(10):1065-1074. DOI: 10.1177/03331024211007789
27. Farzin K, Kheiltash A, Tafakhori A, Nakhjiri NE, Sabet MS, Nayeri ND. The effectiveness of agomelatine on headache severity and frequency in episodic migraine without aura; a parallel randomized controlled trial study. BMC Neurol. 2024;24(1):2. DOI: 10.1186/s12883-023-03516-9
28. Surani M, Yousuf M, Anjum N, Khan S, Hasan G, Hussain S. Topiramate For Migraine Prophylaxis Among Children Aged 5 To 15 Years. J Ayub Med Coll Abbottabad. 2021;33(3):480-483. Available at: https://jamc.ayubmed.edu.pk/index.php/jamc/article/view/7299/3148
29. FDA BOTOX (OnabotulinumtoxinA) Label. ;2010. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/103000s5236lbl.pdf
30. Shah S, Calderon M, Crain N, Pham J, Rinehart J. Effectiveness of onabotulinumtoxinA (BOTOX) in pediatric patients experiencing migraines: a randomized, double-blinded, placebo-controlled crossover study in the pediatric pain population. Reg Anesth Pain Med. 2021;46(1):41-48. DOI: 10.1136/rapm-2020-101605
31. Akbar A, Ford J, Tripathi S. The Use of Botulinum Toxin Type A in Medically Refractory Pediatric Patients With Chronic Daily Headaches and Its Impact on the Quality of Life. J Child Neurol. 2024;39(1-2):55-60. DOI: 10.1177/08830738241227061
32. Oskoui M, Pringsheim T, Billinghurst L, Potrebic S, Gersz EM, Gloss D, *et al.* Practice guideline update summary: Pharmacologic treatment for pediatric migraine prevention. Neurology. 2019;93(11):500-509. DOI: 10.1212/WNL.0000000000008105
33. Vaswani N, Lamba P, Arya V, Lekhwani S. Flunarizine Versus Propranolol in Prophylaxis of Pediatric Migraine: An Open-Label Randomized Trial. Cureus. 2024;16(11):e74563. DOI: 10.7759/cureus.74563
34. Singh S, Srinivasan AV, Banerjee TK, Patel KN, Muchhala SS, Kotak BP. Indian Consensus on the Role of Amitriptyline in Migraine Prophylaxis. Cureus.

2024;16(2):e54270. DOI: 10.7759/cureus.54270
35. Versijpt J, Deligianni C, Hussain M, Amin F, Reuter U, Sanchez-del-Rio M, *et al.* European Headache Federation (EHF) critical re-appraisal and meta-analysis of oral drugs in migraine prevention - part 4: propranolol. J Headache Pain. 2024;25(1):119. DOI: 10.1186/s10194-024-01826-y
36. Fayyazil A, Pezeshki N, Mansuri H, Esnaashari F. Comparing Prophylactic Effect of Levetiracetam, Sodium Valproate, and Propranolol in Pediatric Migraine: A Randomized Clinical Trial. Iran J Child Neurol. 2023;17(4):105-115. DOI: 10.22037/ijcn.v17i1.21330
37. Cutrer FM, Limmroth V, Moskowitz MA. Possible mechanisms of valproate in migraine prophylaxis. Cephalalgia. 1997;17(2):93-100. DOI: 10.1046/j.1468-2982.1997.1702093.x
38. Khani S, Hejazi SA, Yaghoubi M, Sharifipour E. Comparative study of magnesium, sodium valproate, and concurrent magnesium-sodium valproate therapy in the prevention of migraine headaches: a randomized controlled double-blind trial. The Journal of Headache and Pain. 2021;22(1):21. DOI: 10.1186/s10194-021-01234-6
39. Bidabadi E, Elyasi M, Hassanzadeh Rad A, Kazemnezhad E. The Effect of Probiotics on Headaches in Children with Migraine Treated with Sodium Valproate: A Randomized Controlled Clinical Trial. Iran J Child Neurol. 2023;17(2):119-126. DOI: 10.22037/ijcn.v17i2.40369
40. Areberg J, Rosen M, Lindsten A, Dragheim M, Ryding J. Population pharmacokinetics of eptinezumab in paediatric patients with migraine and dose selection for phase 3 paediatric migraine studies. Basic Clin Pharmacol Toxicol. 2024;135(4):512-522. DOI: 10.1111/bcpt.14076
41. Ashina M, Lanteri-Minet M, Pozo-Rosich P, Ettrup A, Christoffersen CL, Josiassen MK, *et al.* Safety and efficacy of eptinezumab for migraine prevention in patients with two-to-four previous preventive treatment failures (DELIVER): a multi-arm, randomised, double-blind, placebo-controlled, phase 3b trial. Lancet Neurol. 2022;21(7):597-607. DOI: 10.1016/S1474-4422(22)00185-5
42. Hershey A, Paiva da Silva Lima G, Pannacciulli N, Mackowski M, Koukakis R, McVige JW. Pharmacokinetics and safety of erenumab in pediatric patients with migraine: A phase I, randomized, open-label, multiple-dose study. Clin Transl Sci. 2024;17(3):e13755. DOI: 10.1111/cts.13755
43. Evers S. CGRP in Childhood and Adolescence Migraine: (Patho) physiological and Clinical Aspects. Curr Pain Headache Rep. 2022;26(6):475-480. DOI: 10.1007/s11916-022-01047-5
44. Greene K, Gentile C, Szperka C, Yonker M, Gelfand A, Grimes B, *et al.* CGRP Monoclonal Antibody use for the Preventive Treatment of Refractory Headache Disorders in Adolescents. Pediatr Neurol. 2021;114:62-67. DOI: 10.1016/j.pediatrneurol.2020.09.014
45. Martami F, Togha M, Seifishahpar M, Ghorbani Z, Ansari H, Karimi T, *et al.* The effects of a multispecies probiotic supplement on inflammatory markers and episodic and chronic migraine characteristics: A randomized double-blind controlled trial. Cephalalgia. 2019;39(7):841-853. DOI: 10.1177/0333102418820102
46. Puliappadamb H, Satpathy A, Mishra B, Maiti R, Jena M. Evaluation of Safety and Efficacy of Add-on Alpha-Lipoic Acid on Migraine Prophylaxis in an Adolescent Population: A Randomized Controlled Trial. J Clin Pharmacol. 2023;63(12):1398-1407. DOI: 10.1002/jcph.2331
47. Sun Q, Xie H, Hao L, Ding J, Hong J, Lin X, *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
48. Powers S, Coffey C, Chamberlin L, Ecklund D, Klingner E, Yankey J, *et al.* Trial of Amitriptyline, Topiramate, and Placebo for Pediatric Migraine. The New England journal of medicine. 2016;376(2):115. DOI: 10.1056/NEJMoa1610384
49. Reidy B, Powers S, Coffey C, Chamberlin L, Ecklund D, Klingner E, *et al.* Multimodal Assessment of Medication Adherence Among Youth With Migraine: An Ancillary Study of the CHAMP Trial. J Pediatr Psychol. 2021;47(4):376-387. DOI: 10.1093/jpepsy/jsab123
50. Reidy B, Peugh J, Hershey A, Coffey C, Chamberlin L, Ecklund D, *et al.* Trajectory of treatment response in the child and adolescent migraine prevention (CHAMP) study: A randomized clinical trial. Cephalalgia. 2022;42(1):44-52. DOI: 10.1177/03331024211033551
51. Powers S, Coffey C, Chamberlin L, Ecklund D, Klingner E, Yankey J, *et al.*

Prevalence of Headache Days and Disability 3 Years After Participation in the Childhood and Adolescent Migraine Prevention Medication Trial. JAMA Netw Open. 2021;4(7):e2114712. DOI: 10.1001/jamanetworkopen.2021.14712

52. Winner P, Kabbouche M, Yonker M, Wangsadipura V, Lum A, Brin MF. A Randomized Trial to Evaluate OnabotulinumtoxinA for Prevention of Headaches in Adolescents With Chronic Migraine. Headache. 2020;60(3):564-575. DOI: 10.1111/head.13754

53. Yaghini O, Hoseini N, Ghazavi MR, Mansouri V, Nasiri J, Moosavian T, *et al.* A Comparative Study on the Efficacy of Coenzyme Q10 and Amitriptyline in the Prophylactic Treatment of Migraine Headaches in Children: A Randomized Controlled Trial. Adv Biomed Res. 2022;11(1):43. DOI: 10.4103/abr.abr_235_20