Review Article

Emerging Pharmacological Therapies for Paediatric Migraine: From Conventional Treatments to CGRP-Targeted Therapie

Gopiarasan Kolamuthu[1], Harini Madhanmohan[1], Nithesh Kumar Haridoss[2]

From, [1]Pharm D Student, [2]Assistant Professor, Department of Pharmacy Practice, KG College of Pharmacy and Research Institute, Villupuram, Tamilnadu - 605 203.

ABSTRACT

Paediatric migraine is a prevalent and disabling neurovascular disorder that substantially impairs academic performance, psychosocial development, and quality of life in children and adolescents. Despite its significant global burden, pharmacological management remains limited by sparse paediatric-specific evidence, high placebo response rates in clinical trials, and reliance on extrapolated adult data. Conventional acute therapies, including non-steroidal anti-inflammatory drugs and triptans, remain the cornerstone of symptomatic management, whereas preventive agents such as topiramate, amitriptyline, propranolol, and flunarizine demonstrate variable efficacy and are frequently constrained by tolerability concerns. The landmark Childhood and Adolescent Migraine Prevention (CHAMP) trial further challenged the effectiveness of traditional preventive therapies by demonstrating no superiority of amitriptyline or topiramate over placebo. Recent advances in migraine neurobiology have identified calcitonin gene-related peptide (CGRP) as a pivotal mediator in trigeminovascular activation and migraine pathophysiology, leading to the development of mechanism-based CGRP-targeted therapies. Anti-CGRP monoclonal antibodies, including erenumab, fremanezumab, galcanezumab, and eptinezumab, together with small-molecule CGRP receptor antagonists (gepants), represent a transformative therapeutic paradigm with improved specificity and favourable tolerability profiles. Emerging paediatric trials such as REBUILD, SPACE, and HEADWAY have provided encouraging preliminary evidence regarding efficacy, pharmacokinetics, and safety in adolescents and children, although long-term developmental safety data remain limited. This review critically examines current pharmacological strategies for paediatric migraine, comparing conventional therapies with emerging CGRP-targeted agents in terms of mechanisms, efficacy, safety, and clinical applicability. Particular emphasis is placed on developmental neurobiology, paediatric pharmacokinetic considerations, methodological limitations of paediatric migraine trials, and future directions in precision-based headache therapeutics. CGRP-targeted therapies hold substantial promise for addressing the unmet therapeutic needs of paediatric migraine; however, rigorous long-term paediatric studies and structured pharmacovigilance remain essential before widespread clinical integration.

Key words: Paediatric migraine, calcitonin gene-related peptide, monoclonal antibodies, gepants, migraine prophylaxis, paediatric neurology, headache disorders, precision medicine, adolescent migraine.

Migraine is a complex, episodic neurovascular disorder characterised by recurrent attacks of moderate-to-severe headache, typically unilateral or bifrontal in distribution, accompanied by nausea, vomiting, photophobia, and phonophobia. It ranks consistently among the top ten causes of years lived with disability in the paediatric age group according to successive iterations of the Global Burden of Disease studies, and represents one of the leading causes of neurological disability across childhood and adolescence worldwide [1]. Prevalence increases substantially with age, rising from approximately 3% in children under ten years to 7.7% in school-age children and exceeding 9% in adolescents, with a notable female predominance emerging at puberty [2]. The condition imposes a considerable burden on affected individuals through school absenteeism, impaired academic performance, reduced social participation, and significant comorbid anxiety and depression [3]. The pharmacological management of paediatric migraine lags considerably behind that of adults. Regulatory approvals of acute and preventive therapies for children remain sparse, and clinical practice is heavily guided by expert consensus and extrapolation from adult data.

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Correspondence to : Dr. H. Nithesh Kumar, Pharm D., Assistant Professor, Department of Pharmacy Practice, KG College of Pharmacy and Research Institute, Villupuram, Tamilnadu – 605203

Email : niteshkumar.h26@gmail.com

This situation is compounded by the biological and clinical heterogeneity of paediatric migraine, which differs from the adult condition across multiple dimensions: attack duration tends to be shorter (as brief as one to two hours in younger children), bilateral frontotemporal location is more common than the classical unilateral distribution, and autonomic features such as pallor, diaphoresis, and gastrointestinal disturbance are more pronounced [4]. These phenotypic differences reflect developmental immaturity of pain-processing pathways, altered nociceptor sensitivity, and an evolving neurobiological substrate that changes throughout childhood and adolescence [5].

The most consequential advancement in migraine pharmacotherapy over the past decade has been the discovery and clinical translation of calcitonin gene-related peptide (CGRP) as the pivotal molecular mediator of migraine pathophysiology. CGRP, a 37-amino-acid neuropeptide predominantly released from trigeminal C-fibres and A-delta fibres, orchestrates the neurogenic inflammation and vasodilation that characterise the headache phase. The development of anti-CGRP monoclonal antibodies and gepants, molecules that either neutralise CGRP or antagonise its receptor, has provided highly selective, mechanism-based tools for migraine prevention and acute treatment, with tolerability profiles particularly attractive for paediatric application [6]. This narrative review critically examines current evidence for conventional pharmacological treatments of paediatric migraine, including acute analgesics, triptans, and preventive agents, alongside emerging evidence for CGRP-targeted therapies in children and adolescents. A comparative analysis of efficacy, safety, and tolerability is presented, with emphasis on the contextual limitations of applying adult trial data to younger patients. Unresolved controversies, evidence gaps, and directions for future paediatric pharmacological research are delineated.

2. EPIDEMIOLOGY AND BURDEN OF PAEDIATRIC MIGRAINE

The global prevalence of migraine in children and adolescents has been estimated at approximately 7.7% for those under 15 years and up to 11% in those aged 15 to 19 years, based on meta-analyses incorporating data from diverse geographic and ethnic populations [1,2]. These figures likely underestimate the true burden, as paediatric migraine frequently goes undiagnosed due to atypical clinical presentation, variable symptom reporting by children, and suboptimal application of International Classification of Headache Disorders (ICHD) criteria, developed primarily on adult populations, to younger patients [7].A critical dimension of the paediatric migraine burden is its impact on neurodevelopmental and psychosocial outcomes. Children with migraine demonstrate significantly higher rates of anxiety disorders, depression, sleep disturbances, and school refusal compared with migraine-free peers [3]. The Paediatric Migraine Disability Assessment (PedMIDAS) scale, validated for children aged 4 to 18 years, consistently identifies substantial disability across academic, social, and recreational domains [8]. Even infrequent episodic migraine can produce disproportionate disability in children relative to adults, attributable in part to the heightened sensitivity of the developing nervous system and the amplified contextual disruption caused by even one or two days of school absence per month.

Established risk factors for paediatric migraine include a positive family history (present in 70–80% of cases), female sex after puberty, sleep disorders, obesity, anxiety, and sedentary lifestyle [9]. Emerging evidence also implicates adverse childhood experiences (ACEs) and chronic psychosocial stress in the pathogenesis and chronification of paediatric migraine, underscoring the biopsychosocial complexity of the condition and the necessity for integrated pharmacological and non-pharmacological management strategies [10].

3. PATHOPHYSIOLOGY OF PAEDIATRIC MIGRAINE: MECHANISMS AND DEVELOPMENTAL CONSIDERATIONS

The pathophysiology of migraine involves a dynamic interplay between genetic susceptibility, cortical excitability, trigeminovascular activation, and central sensitisation. While the core mechanisms are broadly conserved between children and adults, several developmental considerations modulate how these processes manifest and respond to pharmacological intervention in the paediatric brain.

3.1. Cortical Spreading Depression and Neuronal Excitability

Cortical spreading depression (CSD), the electrophysiological correlate of the migraine aura, represents a slowly propagating wave of neuronal and glial depolarisation followed by prolonged suppression of electrical activity [11]. CSD activates trigeminal meningeal afferents, initiating the cascade of peripheral and central sensitisation that culminates in the headache phase. The paediatric brain may exhibit a lower threshold for CSD generation due to developmental differences in GABAergic inhibitory tone, glutamatergic excitatory signalling, and cortical connectivity [12]. This heightened cortical excitability may partly explain why paediatric migraine presents with prominent aura and greater sensitivity to visual and sensory stimuli, even in children who cannot reliably recognise or articulate aura symptoms due to limited introspective capacity.

3.2. Trigeminovascular Activation and CGRP Release

The trigeminovascular system constitutes the primary anatomical substrate for migraine headache generation.

Nociceptive signals arising from the meningeal vasculature are conveyed via first-order trigeminal neurons to the trigeminal nucleus caudalis (TNC) and subsequently relayed to higher cortical and limbic centres via thalamocortical projections [13]. A central molecular event in this process is the release of CGRP from trigeminal C-fibres and A-delta fibres, which promotes meningeal vasodilation, facilitates plasma protein extravasation, induces mast cell degranulation, and amplifies nociceptive signalling at both peripheral and central levels [6]. The significance of CGRP in paediatric migraine is increasingly supported by biomarker studies demonstrating elevated plasma and salivary CGRP levels during ictal and postictal phases in children with migraine compared with headache-free controls [14]. Furthermore, CGRP receptor expression has been identified in the trigeminal ganglia, TNC, and periaqueductal grey matter of the developing nervous system, providing a neuroanatomical rationale for CGRP-targeted therapy across all ages [15]. Importantly, the pharmacokinetic handling of CGRP-targeting agents may differ in children due to developmental differences in hepatic metabolism, renal clearance, and volume of distribution — factors that necessitate dedicated paediatric pharmacokinetic characterisation rather than extrapolation from adult dosing regimens.

3.3. Central Sensitisation and Its Paediatric Implications

Central sensitisation, the amplification of nociceptive processing within the central nervous system resulting in hypersensitivity to pain stimuli, is a critical contributor to migraine chronification and disability. Its clinical hallmark, cutaneous allodynia, has been reported in 60–70% of children with migraine, correlating strongly with headache-related disability and risk of progression to chronic migraine [16]. This high prevalence underscores the urgency of timely and effective preventive treatment to interrupt the sensitisation cycle before functional and structural neuroplastic changes become entrenched. Neuroimaging evidence from paediatric studies using functional MRI and diffusion tensor imaging has demonstrated altered functional connectivity within the default mode network, thalamocortical pain circuits, and descending pain-modulatory pathways in children with migraine compared with controls [17]. These neuroimaging signatures are broadly consistent with adult migraine, though longitudinal data examining how these changes evolve with age, treatment, and disease duration remain limited. (Table 1) summarises the pathophysiological mechanisms of paediatric migraine and their corresponding therapeutic target

Table 1. Pathophysiological mechanisms of paediatric migraine and corresponding therapeutic targets.

Pathophysiological Feature	Mechanism	Paediatric Consideration	Therapeutic Target
Cortical spreading depression (CSD)	The propagating wave of neuronal and glial depolarisation triggers trigeminal afferent activation.	CSD threshold may be lower in the developing brain due to reduced GABAergic inhibitory tone	Topiramate, valproate (Na+ channel blockade; CSD suppression)
Trigeminovascular activation	Release of CGRP, substance P, and PACAP from trigeminal C-fibre and Aδ terminals	CGRP levels are elevated periictally in children; comparable to adult ictal values	Triptans (5-HT1B/1D); anti-CGRP mAbs; gepants
CGRP-mediated neurogenic inflammation	Meningeal vasodilation; mast cell degranulation; plasma protein extravasation; nociceptor sensitisation	CGRP receptor expression confirmed in paediatric trigeminal ganglia and TNC	Erenumab, fremanezumab, galcanezumab, eptinezumab; rimegepant, atogepant
Central sensitisation	Prolonged trigeminovascular input sensitises second-order central neurons; it produces cutaneous allodynia.	Allodynia is reported in 60–70% of paediatric migraineurs; it correlates with disability and chronification risk.	Effective preventive therapy; CBT; amitriptyline (limited evidence)
Serotonergic dysregulation	Reduced interictal serotonin; platelet 5-HT fluctuations may trigger attacks	Paediatric platelet 5-HT studies are limited but broadly consistent with adult findings.	Triptans (5-HT1B/1D agonism); tricyclic antidepressants; SSRIs (limited evidence)
Dopaminergic hypersensitivity	Increased dopaminergic tone contributes to premonitory symptoms (nausea, yawning, irritability)	The premonitory phase is more prominent in children, with frequent nausea and vomiting during attacks.	Dopamine antagonists (metoclopramide, prochlorperazine) as adjunctive agents
Hypothalamic activation	The hypothalamus is activated during the prodromal phase; it modulates descending pain inhibitory pathways.	Autonomic features (pallor, diaphoresis) are more prevalent and pronounced in young children.	CGRP-targeted therapies may indirectly modulate hypothalamic CGRP circuits.
Genetic and epigenetic susceptibility	Polygenic risk; CACNA1A, SCN1A, KCNK18 variants; mitochondrial dysfunction implicated	Family history is positive in ~70–80% of paediatric cases; stronger genetic loading than in adults.	Precision medicine and future gene-stratified therapeutic approaches

CGRP = calcitonin gene-related peptide, CSD = cortical spreading depression, TNC = trigeminal nucleus caudalis, GABA = gamma-aminobutyric acid, CBT = cognitive-behavioural therapy

4. CONVENTIONAL ACUTE PHARMACOLOGICAL THERAPIES

4.1. Non-Opioid Analgesics: NSAIDs and Paracetamol

Non-steroidal anti-inflammatory drugs (NSAIDs), particularly ibuprofen and paracetamol (acetaminophen), represent the first-line agents for acute migraine management in children, endorsed by all major paediatric neurology guidelines [18]. Their mechanisms of action in migraine are multifactorial: ibuprofen inhibits cyclooxygenase (COX)-1 and COX-2 enzymes, reducing prostaglandin E2 synthesis and thereby attenuating peripheral sensitisation of trigeminal nociceptors; paracetamol exerts central COX-3 inhibition and may modulate the endocannabinoid system, though its precise mechanism remains incompletely characterised [19].

The pivotal randomised controlled trial (RCT) by Lewis et al. (2002), enrolling 88 children aged 6 to 18 years, demonstrated significantly superior two-hour pain relief with ibuprofen (10 mg/kg) compared with both paracetamol (15 mg/kg) and placebo, with two-hour headache response rates of 76%, 53%, and 28%, respectively [20]. A subsequent meta-analysis confirmed this superiority, supporting ibuprofen as the preferred first-line agent for paediatric migraine attacks of sufficient severity [21]. Naproxen sodium has demonstrated modest but statistically significant benefits in adolescent RCTs and represents a reasonable alternative for children with ibuprofen intolerance. A critical clinical concern with repeated NSAID and paracetamol use is the risk of medication overuse headache (MOH), defined as headache occurring on 15 or more days per month in the context of analgesic use exceeding defined frequency thresholds [22]. MOH is increasingly recognised in children and adolescents, particularly in those with frequent migraine and inadequate preventive therapy, and substantially complicates management by perpetuating a cycle of escalating analgesic consumption and worsening headache burden. Clinicians should educate patients and families about MOH risk and establish clear limits on acute medication use, generally no more than two to three treatment days per week, as a routine preventive strategy.

4.2. Triptans: Mechanism, Paediatric Evidence, and Limitations

Triptans are selective serotonin 5-HT1B/1D receptor agonists that act at multiple sites within the trigeminovascular pathway to abort migraine attacks. Principal mechanisms include vasoconstriction of dilated meningeal vessels via 5-HT1B receptor activation, inhibition of CGRP and substance P release from trigeminal terminals via presynaptic 5-HT1D receptors, and modulation of central trigeminal neurotransmission at the TNC [23]. Seven triptans are available for clinical use, differing in pharmacokinetic profiles, formulations, lipophilicity, and receptor selectivity.

Translation of triptans to the paediatric setting has been substantially challenged by a high and variable placebo response rate in children. A systematic review of paediatric triptan trials identified 24 RCTs involving over 5,000 participants, consistently demonstrating placebo response rates of 40–58% in children compared with approximately 20–30% in adults, a difference that statistically confounds the detection of drug-placebo separation [24]. This amplified placebo response reflects the self-limiting nature of paediatric migraine attacks, the soothing effects of trial participation and caregiver attention, and methodological features including single-attack designs and assessment at fixed timepoints. Consequently, many paediatric triptan RCTs have failed to demonstrate statistical superiority over placebo on their primary endpoints, despite numerical trends favouring active treatment. Among currently FDA-approved triptans for paediatric use, sumatriptan nasal spray (approved for ages 12 and older, 2015), rizatriptan (approved for ages 6 and older, 2018, weight-based dosing), and almotriptan (approved for ages 12 to 17, 2009) are the most widely prescribed. The landmark trial of nasal sumatriptan by Winner et al. (2000) in 653 adolescents aged 12 to 17 years demonstrated significant pain relief at two hours with the 20 mg formulation, establishing the nasal route as preferable for children prone to emesis during attacks [25]. Rizatriptan was evaluated in 296 children aged 6 to 17 years by Ahonen et al. (2004), where the 10 mg dose produced numerically higher pain-free rates than placebo (32% vs 28%) but did not achieve statistical significance, reflecting weight-based dosing heterogeneity across the paediatric age range [26]. Almotriptan demonstrated significant pain-free rates in adolescents in the Linder et al. (2008) trial, with a notably favourable tolerability profile attributable to high oral bioavailability and reduced vasoconstrictive potency compared with sumatriptan [27].

Triptan-class safety concerns in children include vasoconstrictive events (chest pressure, paraesthesia), somnolence, dizziness, and the potential for serotonin syndrome when combined with selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs). Cardiovascular contraindications apply to paediatric prescribing equally as to adults, though such conditions are exceptionally rare in children. Long-term triptan use also carries MOH risk, and structured frequency limits should be incorporated into prescribing counselling.

5. CONVENTIONAL PREVENTIVE PHARMACOLOGICAL THERAPIES

Preventive therapy is indicated for children with frequent episodic migraine (four or more headache days per month), significant functional disability (PedMIDAS score ≥30), acute medication overuse, or failure of adequate acute therapy, in accordance with guidelines from the American Headache

Society (AHS) and European Headache Federation (EHF) [18,28]. Historically, preventive pharmacotherapy for paediatric migraine has comprised tricyclic antidepressants (amitriptyline), anticonvulsants (topiramate, valproate), beta-blockers (propranolol), and calcium channel blockers (flunarizine), with the evidence base for each derived predominantly from small RCTs and open-label studies of variable methodological quality.

5.1. Topiramate

Topiramate exerts anti-migraine effects through multiple mechanisms: inhibition of voltage-gated sodium channels, potentiation of GABA-A receptor activity, antagonism of kainate and AMPA glutamate receptors, and inhibition of carbonic anhydrase isoforms II and IV [29]. Together, these actions reduce cortical excitability, attenuate trigeminovascular activation, and suppress CSD propagation. Clinical efficacy in adolescent migraine prevention was established by the Winner et al. (2005) RCT (n = 162, ages 12–17), which demonstrated a significantly higher 50% responder rate with topiramate 100 mg/day compared with placebo (72% vs 44%; $p < 0.001$) [30]. Topiramate received FDA approval for migraine prophylaxis in adolescents aged 12 years and older in 2014.

However, clinical utility in the paediatric setting is substantially limited by its adverse effect profile. Cognitive dysfunction, encompassing slowed processing speed, word-finding difficulties, and memory impairment (the so-called "dopamax" phenomenon), is particularly concerning in children undergoing active neurological development [31]. Additional adverse effects include anorexia and weight loss, paraesthesia, metabolic acidosis, nephrolithiasis, and a small risk of narrow-angle glaucoma. Subsequent demonstration of no superiority over placebo in the CHAMP trial (2017) has considerably moderated enthusiasm for topiramate as a first-choice preventive agent in paediatric practice, though it retains utility as a second-line option when comorbidities such as epilepsy or obesity are present.

5.2. Amitriptyline

Amitriptyline, a tricyclic antidepressant, has been widely used for paediatric migraine prevention based on its presumed mechanisms of norepinephrine and serotonin reuptake inhibition, sodium channel blockade, and downstream modulation of central pain-processing circuits [32]. Before 2017, amitriptyline was arguably the most frequently prescribed preventive agent for paediatric migraine in North America, administered off-label at doses typically ranging from 0.1 to 0.5 mg/kg/day at night, supported by retrospective cohort data and a single small RCT by Hershey et al. (2000) demonstrating significant headache frequency reduction.

The seminal CHAMP trial, published in the New England Journal of Medicine in 2017, fundamentally challenged this practice [33]. This multicentre, double-blind, placebo-controlled RCT enrolled 328 children and adolescents aged 8 to 17 years with high-frequency episodic or chronic migraine, randomised to amitriptyline (maximum 1 mg/kg/day), topiramate (maximum 2 mg/kg/day), or placebo over 24 weeks. The primary outcome, a reduction of 50% or more in headache days, was achieved in 52%, 55%, and 61% of the amitriptyline, topiramate, and placebo arms, respectively, with no statistically significant difference between active agents and placebo. The trial was stopped early for futility. Moreover, serious adverse events, including mood disorders and suicidal ideation with topiramate, and QTc prolongation with amitriptyline, were more frequent in the active treatment arms [33]. The CHAMP trial represents the most consequential paediatric migraine prevention study to date and demands a fundamental re-evaluation of conventional preventive prescribing in children.

5.3. Propranolol and Other Beta-Blockers

Propranolol, a non-selective beta-adrenoreceptor antagonist, has been used for paediatric migraine prevention since the 1970s based on early open-label data and small RCTs demonstrating reductions in attack frequency [34]. Its presumed anti-migraine mechanisms include attenuation of catecholaminergic hyperreactivity, inhibition of 5-HT2-mediated platelet aggregation, and modulation of cortical excitability. A Cochrane review identified only four adequately controlled paediatric trials, with inconsistent findings and high risk of bias [35]. Contraindications include asthma, insulin-dependent diabetes mellitus, and significant cardiovascular abnormalities. At doses of 1–4 mg/kg/day, propranolol remains a reasonable off-label option for adolescents with comorbid anxiety or autonomic dysregulation, though it should not be considered a first-line preventive agent given the limited evidence base.

5.4. Flunarizine and Calcium Channel Blockers

Flunarizine, a selective calcium channel blocker with additional dopaminergic antagonist and histamine H1-blocking properties, holds a more favourable evidence base than most other conventional preventive agents in children, with multiple European and Asian RCTs demonstrating significant reductions in migraine frequency and severity in paediatric cohorts [36]. Despite this evidence, flunarizine is not approved by the FDA, limiting its use to Europe, Asia, and Latin America. Adverse effects of clinical significance include weight gain, sedation, depression, and extrapyramidal effects with prolonged use, the latter being particularly concerning in the developing nervous system. Valproate, while possessing a reasonable adult evidence base, carries teratogenic risk, hepatotoxicity potential, and associations with polycystic ovarian syndrome in adolescent females, considerations that substantially restrict its paediatric use and necessitate careful individualised risk-benefit assessment [37].

6. CGRP-TARGETED THERAPIES: MECHANISMS, CLASSIFICATION, AND PHARMACOLOGY

The validation of CGRP as a therapeutic target in migraine represents the most significant mechanistic advance in headache medicine since the introduction of triptans in the 1990s. Two distinct pharmacological classes targeting the CGRP pathway have been clinically translated: anti-CGRP monoclonal antibodies (mAbs), which provide sustained monthly or quarterly prevention, and small-molecule CGRP receptor antagonists (gepants), which offer oral bioavailability and suitability for both acute and preventive administration.

6.1. Anti-CGRP Monoclonal Antibodies: Mechanisms and Classification

Four anti-CGRP monoclonal antibodies have received FDA approval for adult migraine prevention: erenumab (Aimovig; targeting the CGRP receptor), fremanezumab (Ajovy; targeting the CGRP ligand), galcanezumab (Emgality; targeting the CGRP ligand), and eptinezumab (Vyepti; administered intravenously, targeting the CGRP ligand) [38]. The molecular distinction between receptor-targeting and ligand-targeting strategies carries pharmacological relevance: erenumab, as a fully human IgG2 antibody, may produce different immunological responses than the humanised IgG frameworks of fremanezumab (IgG2a) and galcanezumab (IgG4), and blockade of the CGRP receptor across its multiple tissue distributions may have different physiological consequences than neutralisation of the circulating CGRP ligand itself.

The large molecular weight (~150 kDa) of these antibodies confers properties of particular relevance to paediatric pharmacology: minimal CNS penetration, prolonged half-life enabling monthly or quarterly subcutaneous dosing, and metabolism via non-saturable proteolytic degradation rather than hepatic cytochrome P450 pathways, reducing drug-drug interaction potential [39]. Immunogenicity, the development of anti-drug antibodies (ADAs), is an important long-term consideration for any biologic therapy and may affect both efficacy (via neutralising antibodies) and safety (via hypersensitivity reactions). ADA incidence rates in adult trials have been low (approximately 1–6%), though whether the more reactive paediatric immune system would mount more pronounced immunogenic responses to repeated antibody administration requires systematic investigation [40].

6.2. Gepants: Oral CGRP Receptor Antagonists

The gepants are orally bioavailable, small-molecule CGRP receptor antagonists initially developed as acute migraine therapies. Unlike triptans, gepants achieve their therapeutic effect through competitive receptor antagonism without vasoconstriction, rendering them devoid of the cardiovascular class-specific contraindications associated with 5-HT1B agonism [41]. Three gepants have received FDA approval: ubrogepant (Ubrelvy) and rimegepant (Nurtec ODT) for acute treatment, with rimegepant additionally approved for preventive use at an every-other-day dosing schedule; and atogepant (Qulipta) for preventive therapy. A fourth gepant, zavegepant (Zavzpret), approved as a nasal spray for acute migraine, may hold particular promise for paediatric patients with nausea-dominant attacks.

Gepants are metabolised principally via hepatic CYP3A4 (rimegepant, ubrogepant) or CYP3A4 and CYP2C8 pathways (atogepant), and clinically significant drug interactions with strong CYP3A4 inhibitors or inducers, including macrolide antibiotics, antiepileptic drugs, and azole antifungals, are directly relevant to the paediatric population in whom antiepileptic co-prescribing is common [42]. The small molecular size of gepants permits greater CNS penetration than antibodies, and preclinical evidence suggests central anti-nociceptive effects via CGRP receptor antagonism within the TNC and periaqueductal grey matter, a property potentially important for addressing central sensitisation. A dual-action property of rimegepant is particularly clinically relevant: every-other-day administration in the RECOVER trial (2021) reduced monthly migraine days by 4.3 compared with 2.5 for placebo ($p < 0.0001$), establishing it as the first oral preventive migraine therapy with simultaneous acute and preventive FDA approval [43]. Whether this dual utility translates effectively to the paediatric population, in the context of dedicated pharmacokinetic characterisation and dose-finding, is a critical question for ongoing trials.

7. CLINICAL EVIDENCE FOR CGRP-TARGETED THERAPIES IN ADULTS: CONTEXT FOR PAEDIATRIC EXTRAPOLATION

The adult clinical trial programme for anti-CGRP mAbs and gepants constitutes the primary evidence base from which paediatric efficacy and safety inferences are currently drawn. A critical appraisal of this evidence, with explicit acknowledgement of the limitations of direct extrapolation to children, is essential for informed clinical decision-making.

7.1. Anti-CGRP Monoclonal Antibodies: Key Adult Trial Evidence

Erenumab was evaluated in the ARISE (episodic migraine; n = 577) and STRIVE (episodic migraine; n = 955) phase 3 trials, demonstrating monthly migraine day (MMD) reductions of 2.9 and 3.2 days over placebo, with 50% responder rates of approximately 43–50% [39,44]. The LIBERTY trial (2018) specifically evaluated erenumab in patients who had failed two to four prior preventive therapies, demonstrating significant MMD reduction and disability improvement at 140 mg, a population particularly relevant to paediatric patients refractory to conventional treatments [45]. Fremanezumab, evaluated in the HALO CM (chronic migraine; n = 1,130) and HALO EM

(episodic migraine; n = 875) trials, demonstrated MMD reductions of 4.6 days (monthly dosing) and 3.4 days (quarterly dosing) over placebo for chronic migraine prevention [46]. Galcanezumab demonstrated MMD reductions of approximately 4.7 days in the EVOLVE-1 and EVOLVE-2 trials, including significant efficacy in treatment-refractory patient subgroups [47].

Collectively, adult anti-CGRP mAb trials demonstrate favourable tolerability characterised primarily by injection-site reactions, nasopharyngitis, and, particularly for erenumab, constipation (approximately 3–10% of patients), attributable to CGRP's physiological role in intestinal motility regulation [48]. Concerns regarding potential cardiovascular effects of CGRP pathway blockade, given CGRP's vasodilatory role in ischaemic preconditioning, have been raised in the context of Raynaud's phenomenon and hypertension, though no consistent signal has emerged across large adult trial datasets [49]. Long-term open-label extension data spanning five or more years have not identified major emerging safety signals in adult populations, though these studies inherently select for tolerant responders.

7.2. Gepants in Adults: Acute and Preventive Evidence

Rimegepant (75 mg orally disintegrating tablet) was evaluated in three phase 3 acute migraine trials collectively enrolling over 3,500 adults, demonstrating consistent two-hour pain-free rates of 19–21% versus 10–12% for placebo, with no cardiovascular adverse effects of the triptan class [41,43]. Atogepant was evaluated in the ADVANCE phase 3 trial (n = 910), demonstrating dose-dependent MMD reductions of 3.7–4.2 days over placebo, with the 60 mg once-daily dose approved by the FDA in 2023 for preventive treatment [51]. The ACHIEVE II trial confirmed the acute efficacy of ubrogepant, with two-hour pain-free rates of 19.2% versus 11.7% for placebo [50].

A clinically important advantage of gepants over triptans is the absence of vasoconstrictive effects, rendering them theoretically safe in patients with vascular risk factors, a consideration of growing relevance for adolescent patients with complex medical comorbidities. The hepatotoxicity signal identified with the earlier gepant telcagepant, which was discontinued in development, necessitated rigorous hepatic safety monitoring throughout subsequent gepant development programmes [52]. Contemporary gepants have not demonstrated hepatotoxic signals at recommended doses in clinical trials, though regulatory requirements mandate liver function assessment in patients with hepatic impairment.

8. EMERGING EVIDENCE FOR CGRP-TARGETED THERAPIES IN PAEDIATRIC MIGRAINE

The paediatric evidence base for CGRP-targeted therapies is in its early but rapidly evolving phase. Driven by transformative adult trial data, the unmet clinical need exposed by the CHAMP trial, and regulatory mandates under the FDA Paediatric Research Equity Act (PREA), pharmaceutical sponsors have initiated or completed multiple dedicated paediatric trials whose results will substantially reshape preventive treatment for children with migraine.

8.1. Galcanezumab: REBUILD Paediatric Trial

The REBUILD trial represents the most advanced dedicated paediatric RCT for an anti-CGRP mAb published to date. This double-blind, placebo-controlled, phase 3 trial enrolled approximately 130 children and adolescents aged 6 to 17 years with episodic or chronic migraine, randomised 1:1 to galcanezumab (weight- and age-adjusted dosing; 120 mg monthly for adolescents) or placebo over 12 weeks, followed by an open-label extension phase [53]. Preliminary results presented at international headache congresses in 2023 indicated statistically significant reductions in mean monthly migraine and headache days in the galcanezumab arm compared with placebo, directionally consistent with adult trial findings. A paediatric New Drug Application (NDA) was filed by the sponsor with the FDA in 2024 based on REBUILD data, and regulatory approval for adolescents would establish the first FDA-approved preventive biologic therapy for paediatric migraine.

8.2. Fremanezumab: The SPACE Trial

The SPACE (Study of Fremanezumab in Paediatric Patients Aged 6 to Less Than 18 Years) trial is a phase 3, randomised, double-blind, placebo-controlled study evaluating the efficacy and safety of monthly versus quarterly fremanezumab in paediatric migraine across the 6 to 17 year age range [54]. Weight-appropriate dosing algorithms were derived from population pharmacokinetic modelling to achieve drug exposures comparable to approved adult doses. Preliminary safety and tolerability data presented through 2023–2024 have been reassuring, with no unexpected adverse event profiles beyond the established adult safety database. Final efficacy results are anticipated for publication in 2025–2026. The enrolment of children as young as 6 years is particularly noteworthy, given the historical underrepresentation of the youngest age group in all paediatric migraine trials.

8.3. Erenumab: Adolescent Pilot and Ongoing Studies

Erenumab's paediatric programme has included an adolescent pharmacokinetic and safety study (NCT03777163) evaluating 70 mg and 140 mg monthly subcutaneous injections in adolescents aged 12 to 17 years with high-frequency or chronic migraine [55]. Published pharmacokinetic data (2022–23) demonstrated that adolescent erenumab exposure parameters, including maximum serum concentration, area under the concentration-time curve, and clearance, were broadly comparable to adult values, supporting the feasibility of adult dosing regimens in adolescents without major dose adjustment;

however, the study was not powered for efficacy evaluation. A full phase 3 RCT in adolescents is ongoing, with anticipated completion in 2026. Pharmacokinetic and safety data in children under 12 remain absent, reflecting the general paucity of monoclonal antibody data in pre-pubertal children.

8.4. Gepants in Adolescents: Rimegepant and Atogepant

Gepants present a particularly attractive option for adolescent migraine given their oral bioavailability, absence of vasoconstriction risk, and dual acute-preventive utility. A dedicated pharmacokinetic and safety study of rimegepant in adolescents aged 12 to 17 years (n = 18), published by Ho et al. in 2023, demonstrated that single-dose rimegepant 75 mg produced plasma concentration profiles comparable to adult data (mean Cmax 2.1 ng/mL; AUC0-inf 17.8 ng·h/mL) with no clinically significant safety signals [56]. While this study was not designed to assess efficacy, the favourable pharmacokinetic data support the design of a full phase 3 efficacy trial in adolescents. The HEADWAY trial evaluating atogepant in adolescents with episodic migraine is ongoing, with expected completion in 2025–2026. Zavegepant nasal spray, potentially advantageous in paediatric patients with significant nausea or vomiting, has not yet entered formal paediatric clinical evaluation. (Table 2) summarises key clinical trials of pharmacological agents for paediatric migraine.

9. COMPARATIVE ANALYSIS: CONVENTIONAL THERAPIES VERSUS CGRP-TARGETED AGENTS IN PAEDIATRIC MIGRAINE

A rigorous comparative analysis of conventional and CGRP-targeted therapies in the paediatric context must encompass multiple dimensions: mechanistic specificity, clinical efficacy, tolerability, regulatory status, formulation characteristics, pharmacokinetic data in children, and cost-effectiveness. (Table 3) presents a comprehensive comparative pharmacological profile across these drug classes.

Table 2. Key clinical trials of pharmacological agents for paediatric migraine (2000–2026).

Study (Year)	Drug / Intervention	Age (years)	n	Primary Endpoint	Key Finding	Limitations / Status
Lewis et al. (2002) [20]	Ibuprofen vs paracetamol vs placebo	6–18	88	2-h headache relief	Ibuprofen superior: 76% vs 53% for paracetamol; both superior to placebo	Small sample; crossover design
Winner et al. (2000) [25]	Sumatriptan nasal spray 20 mg	12–17	653	2-h headache relief	Significant improvement vs placebo at 2 h	Adolescents only; high placebo response (~58%)
Ahonen et al. (2004) [26]	Rizatriptan 5 mg vs 10 mg	6–17	296	2-h pain-free rate	10 mg: 32% pain-free; placebo: 28% (NS primary endpoint)	NS primary endpoint; high placebo response; weight-dosing heterogeneity
Winner et al. (2005) [30]	Topiramate 100 mg/day	12–17	162	50% responder rate (migraine days)	72% vs 44% placebo ($p<0.001$)	Short duration (16 weeks); frequent cognitive adverse events
Powers et al. / CHAMP (2017) [33]	Amitriptyline vs topiramate vs placebo	8–17	328	≥50% reduction in headache days	No superiority over placebo for either active arm; trial stopped early for futility	Landmark negative trial; high placebo response; redefines preventive practice
Kacperski et al. / REBUILD (2023) [53]	Galcanezumab (CGRP mAb)	6–17	~130	MMD reduction at 3 months	Statistically significant MMD reduction vs placebo (preliminary)	Full peer-reviewed publication pending; paediatric NDA filed 2024
Rosen et al. / SPACE (2022–24) [54]	Fremanezumab (CGRP mAb)	6–17	~200 (target)	MMD reduction over 12 weeks	Phase 3 ongoing; interim safety data favourable	Incomplete dataset; final results expected 2025–26
Ho et al. (2023) [56]	Rimegepant 75 mg (PK study)	12–17	18	PK profile and safety	Adult-comparable PK; well tolerated; no significant safety signals	PK/safety study only; efficacy not assessed
HEADWAY trial (2024–ongoing)	Atogepant (preventive gepant)	12–17	~200 (target)	MMD reduction over 12 weeks	Ongoing; results expected 2025–26	No results published; primary endpoint not yet assessed

MMD = monthly migraine days, NS = not significant, NDA = New Drug Application, PK = pharmacokinetics; RCT = randomised controlled trial, mAb = monoclonal antibody.

Table 3. Comparative pharmacological profile of conventional and CGRP-targeted therapies for paediatric migraine.

Drug Class / Agent	Mechanism of Action	Paediatric Evidence	Efficacy (Primary Endpoint)	Safety Concerns	Paediatric Approval (FDA/EMA)
CONVENTIONAL ACUTE THERAPIES					
Ibuprofen	COX-1/2 inhibition; prostaglandin synthesis blockade	Multiple RCTs (Hämäläinen 1997; Lewis et al. 2002) [20,21]	76% pain relief at 2 h vs 53% for paracetamol [20]	GI upset; renal risk with chronic overuse; MOH risk (>15 days/month)	Yes (OTC; ≥6 months)
Paracetamol (acetaminophen)	Central COX inhibition; endocannabinoid modulation	Limited dedicated RCTs; commonly used in combination	Modest benefit vs placebo; inferior to ibuprofen [21]	Hepatotoxicity at supratherapeutic doses; MOH risk	Yes (OTC; ≥2 years)
Sumatriptan nasal spray	5-HT1B/1D agonist; cranial vasoconstriction; CGRP and substance P release inhibition	Winner et al. (2000) RCT; n=653; ages 12–17 [25]	Significant 2-h pain relief; 20 mg superior to placebo [25]	Chest tightness; somnolence; rhinitis; cardiovascular contraindications	Yes (FDA 2015; ≥12 years)
Rizatriptan	5-HT1B/1D agonist (oral tablet/ODT); weight-based dosing	Ahonen et al. (2004) RCT; n=296; ages 6–17 [26]	2-h pain-free: 32% vs 28% placebo; primary endpoint NS [26]	Dizziness; fatigue; nausea; serotonin syndrome risk with SSRIs/SNRIs	Yes (FDA 2018; ≥6 years)
Almotriptan	5-HT1B/1D agonist; high oral bioavailability; reduced vasoconstrictive potency	Linder et al. (2008) RCT; n=866; ages 12–17 [27]	Significant pain-free rates vs placebo; well tolerated [27]	Generally well tolerated; CYP3A4/2D6 metabolism	Yes (FDA 2009; 12–17 years)
CONVENTIONAL PREVENTIVE THERAPIES					
Amitriptyline	Tricyclic antidepressant; norepinephrine/serotonin reuptake inhibition; Na+ channel blockade	CHAMP trial (2017); n=328; ages 8–17 [33]	No superiority over placebo; CHAMP trial stopped for futility [33]	Anticholinergic effects; sedation; QTc prolongation; suicidal ideation risk	Off-label (no FDA/EMA paediatric approval)
Topiramate	Na+ channel blockade; GABA-A potentiation; AMPA/kainate antagonism; carbonic anhydrase inhibition	CHAMP (2017); Winner et al. (2005) RCT; n=162; ages 12–17 [30,33]	72% vs 44% responders vs placebo (Winner 2005); no superiority in CHAMP [30,33]	Cognitive slowing; anorexia; paraesthesia; nephrolithiasis; teratogenicity	Yes (FDA 2014; ≥12 years for prophylaxis)
Propranolol	Non-selective β1/β2-adrenoreceptor antagonist; serotonergic modulation	Small RCTs (Forsythe et al. 1984; Ludvigsson 1974); Cochrane review [34,35]	Modest and inconsistent reduction in attack frequency [35]	Bradycardia; bronchospasm; fatigue; depression; masks hypoglycaemia symptoms	Off-label; not FDA-approved for paediatric migraine
Flunarizine	Selective Ca2+ channel blocker; dopamine antagonist; H1 antihistaminic properties	Multiple European and Asian RCTs (Sorge 1988; Guidetti et al. 1987) [36]	Significant reduction in attack frequency vs placebo across multiple trials [36]	Weight gain; sedation; depression; extrapyramidal effects (tardive dyskinesia)	Not FDA-approved; approved in Europe/Asia/Latin America
CGRP-TARGETED THERAPIES					
Erenumab	Anti-CGRP receptor mAb (fully human IgG2)	Phase 2/3 adolescent PK/safety study (NCT03777163; 2022–23) [55]; phase 3 RCT ongoing	Adults: ~50% responder rate; MMD reduction ~3.2 days/month [44]	Constipation; injection-site reactions; rare hypertension; immunogenicity	FDA-approved adults (2018); paediatric phase 3 ongoing
Fremanezumab	Anti-CGRP ligand mAb (humanised IgG2a)	Phase 3 SPACE trial (ages 6–17); preliminary safety data favourable	Adults: MMD reduction ~3.4 days/month (quarterly) [46]	Injection-site reactions; generally well tolerated in adult trials [46]	FDA-approved adults (2018); paediatric approval pending (SPACE)

		[54]			
Galcanezumab	Anti-CGRP ligand mAb (humanised IgG4)	REBUILD phase 3 RCT (ages 6–17; n≈130); paediatric NDA filed 2024 [53]	Adults: MMD reduction ~4.7 days/month (EVOLVE-1/-2) [47]; paediatric results significant [53]	Injection-site reactions; upper respiratory tract infections [47]	FDA-approved adults (2019); paediatric NDA filed 2024
Rimegepant	Oral CGRP receptor antagonist (gepant; ODT); acute and preventive use	Phase 1 PK/safety study in adolescents (12–17 years; n=18; Ho et al. 2023) [56]	Adults: 2-h pain-free 21% vs 11% placebo (RECOVER); also approved preventively [43,50]	Nausea; LFT surveillance required; avoid strong CYP3A4 inhibitors/inducers	FDA-approved adults (2020); adolescent phase 3 pending PK data
Ubrogepant	Oral CGRP receptor antagonist (gepant); acute use only	No published paediatric trials as of 2025	Adults: 2-h pain-free 19.2% vs 11.7% placebo (ACHIEVE II) [50]	Nausea; somnolence; CYP3A4 drug interactions	FDA-approved adults (2019); no paediatric data
Atogepant	Oral CGRP receptor antagonist (gepant); preventive use	Phase 3 HEADWAY trial in adolescents (ongoing; completion 2025–26)	Adults: MMD reduction ~4.2 days/month (ADVANCE) [51]	Nausea; constipation; fatigue; CYP3A4/2C8 interactions	FDA-approved adults (2023); paediatric HEADWAY trial ongoing

mAb = monoclonal antibody, FDA = US Food and Drug Administration, EMA = European Medicines Agency, RCT = randomised controlled trial, MMD = monthly migraine days, GI = gastrointestinal, MOH = medication overuse headache, NS = not significant, NDA = New Drug Application, ODT = orally disintegrating tablet.

9.1. Mechanistic Specificity and Therapeutic Precision

Conventional preventive agents such as topiramate, amitriptyline, and propranolol act through broad, non-specific mechanisms that affect multiple neurotransmitter systems simultaneously — a property that contributes to both their therapeutic versatility and their adverse effect burden. In contrast, CGRP-targeted therapies are exquisitely mechanism-specific, acting on a single molecular pathway directly validated in migraine pathophysiology. This therapeutic precision translates to a narrower and more predictable adverse effect profile, as off-target effects on histaminergic, muscarinic, dopaminergic, adrenergic, or GABAergic systems are absent. For the developing paediatric brain, this distinction is potentially critical: the receptor promiscuity of tricyclic antidepressants, for example, affects neurochemical systems undergoing active developmental maturation, raising theoretical concerns about long-term neurodevelopmental consequences that do not apply to CGRP-targeted therapies.

9.2. Efficacy Comparison and the Challenge of Placebo Response

A fundamental methodological challenge in comparing treatment effects across paediatric migraine trials is the consistently high and variable placebo response rate. Pooled analyses of paediatric preventive migraine trials report placebo response rates of 40–60% for a 50% reduction in headache frequency, substantially higher than the 20–30% commonly observed in adult studies [57]. This amplified placebo response reflects not only natural history effects (spontaneous resolution or improvement being more common in children than adults) but also non-specific benefits of increased clinical attention, education, and behavioural modification embedded within trial participation. The CHAMP trial's finding that both amitriptyline and topiramate performed no better than placebo, despite the latter's established adult efficacy, may thus partly reflect this powerful paediatric placebo response overwhelming any drug-specific treatment effect, rather than indicating true pharmacological futility [33]. CGRP-targeted therapy trials will face the same methodological challenge, and future paediatric trial designs must incorporate strategies to maximise signal detection in the context of high baseline placebo response.

9.3. Safety and Tolerability: A Critical Paediatric Perspective

The safety profiles of anti-CGRP therapies in children remain incompletely characterised given the early stage of paediatric clinical evaluation. Several theoretical concerns specific to the paediatric context warrant careful prospective evaluation. CGRP plays important physiological roles beyond migraine pathophysiology: it is a potent vasodilator involved in cardiovascular regulation, a modulator of bone metabolism (promoting osteogenesis and inhibiting osteoclast activity), a

regulator of gastrointestinal motility, and a mediator of sensory neuronal development [58]. In growing children, chronic suppression of CGRP signalling through long-term antibody administration could theoretically affect bone mineral density, skeletal development, and cardiovascular responsiveness in ways not yet detectable in the relatively short-term adult or paediatric clinical trials conducted to date.

Constipation, the most consistent adverse effect differentiating erenumab from other anti-CGRP mAbs in adults, warrants particular attention in children, given CGRP's physiological role in enteric nervous system modulation and the prevalence of functional gastrointestinal disorders in the paediatric migraine population. The immunological consequences of repeated monthly subcutaneous administration in children — whose immune systems are actively maturing — represent an additional under-investigated safety domain. Long-term registry data and pharmacovigilance programmes will be essential to fully characterise these risks in paediatric populations following any regulatory approval.

10. ADULT VERSUS PAEDIATRIC MIGRAINE: CRITICAL DIFFERENCES IN TREATMENT EVIDENCE

A rigorous appraisal of paediatric migraine pharmacotherapy requires explicit acknowledgement of the multiple domains in which children and adults fundamentally differ, rendering the uncritical extrapolation of adult trial findings to paediatric practice both scientifically unjustified and potentially hazardous. Key differences span clinical, neurobiological, pharmacokinetic, and methodological dimensions. From a clinical standpoint, paediatric migraines are on average shorter in duration, more commonly bilateral, and more frequently associated with prominent nausea, vomiting, and autonomic features than adult migraines, reflecting developmental differences in trigeminovascular anatomy and central pain-modulating systems [4,5]. These phenotypic differences affect both the likelihood of therapeutic response and the detection of treatment effects at standardised timepoints used in adult-validated endpoints. The ICHD-3 criteria accommodate paediatric differences by permitting shorter attack duration criteria for children (1 to 72 hours versus 4 to 72 hours in adults), though the operationalisation of these criteria in clinical trials has been inconsistent [7].

Pharmacokinetically, children exhibit significantly higher hepatic metabolic activity per unit body weight, particularly for CYP3A4 and CYP2D6 substrates, relative to adults until mid-adolescence, higher renal clearance, a different volume of distribution due to higher total body water content, and lower plasma protein binding in younger children [59]. These differences collectively affect plasma concentration profiles, efficacy thresholds, and optimal dosing frequency, necessitating weight-based and age-stratified dosing rather than adult dose replication. For monoclonal antibodies, adolescent pharmacokinetic studies have generally demonstrated broadly comparable exposure to adults, attributable to the non-CYP-dependent clearance of large biologics, though data in pre-pubertal children remain sparse. For gepants, the CYP3A4-dependent clearance pathway may result in higher drug clearance rates in pre-adolescent children, potentially necessitating dose adjustment.

Methodologically, paediatric migraine trials face unique challenges that systematically reduce detectable drug-placebo differences and limit generalisability: the amplified placebo response rates already discussed, challenges of headache diary compliance in younger children, difficulties obtaining reliable pain ratings in pre-adolescents, the influence of parental anxiety on outcome reporting, and comparatively smaller trial sample sizes relative to adult programmes. The International Headache Society (IHS) has published specific guidelines for paediatric headache clinical trials acknowledging these challenges and proposing methodological adaptations, though widespread adoption remains incomplete [60]. Future paediatric trials should incorporate validated paediatric-specific outcome measures, electronic diary platforms, and longer washout periods that accommodate the slower natural resolution trajectory of migraine in children.

11. CLINICAL IMPLICATIONS FOR PAEDIATRIC PRACTICE

Translating emerging evidence for CGRP-targeted therapies into clinical paediatric practice requires a nuanced, individualised approach guided by disease severity, prior treatment history, comorbidities, patient and family preferences, and the evolving but still incomplete paediatric evidence base. For acute migraine management, ibuprofen remains the first-line agent for children of all ages, with nasal sumatriptan or weight-dosed rizatriptan representing evidence-based options for moderate-to-severe attacks in eligible children aged 12 and 6 years, respectively. Clinicians should be vigilant for MOH and routinely enforce frequency limits on acute medication use. Antiemetics (metoclopramide, prochlorperazine, ondansetron) should be co-prescribed when nausea or vomiting significantly impairs medication absorption or quality of life, in recognition of their role in managing the prominent autonomic component of the paediatric migraine attack.

For preventive therapy, the landscape has been fundamentally reshaped by the CHAMP trial. Conventional preventive agents retain a role in selected patients, topiramate in adolescents with comorbid epilepsy or obesity-associated headache; amitriptyline in those with comorbid anxiety or significant sleep dysfunction, with appropriate baseline electrocardiographic (ECG) monitoring; propranolol in those with comorbid anxiety or postural tachycardia syndrome, but

should not be prescribed as default first-line agents for uncomplicated migraine prevention. Families must be counselled regarding the CHAMP evidence and the high placebo response rate in the context of a comprehensive headache management programme [33]. Non-pharmacological interventions, cognitive-behavioural therapy (CBT), biofeedback, and lifestyle modification (regular sleep, adequate hydration, dietary rhythm), have a robust independent evidence base in paediatric migraine and should be integrated into all management plans [61].

In centres with access to clinical trial participation, enrolment of appropriate paediatric patients in ongoing CGRP-targeted therapy trials should be actively considered, both to advance the evidence base and to provide access to potentially efficacious novel therapies under structured research conditions. For adolescents who have failed two or more preventive therapies and whose migraine burden remains severe, off-label use of anti-CGRP mAbs may be considered by specialist paediatric neurologists following detailed discussion of the current evidence base, the unapproved paediatric status, potential theoretical risks, and the absence of long-term paediatric safety data. Any off-label prescribing should be accompanied by structured monitoring protocols, informed consent, and systematic documentation, ideally within a registry framework to contribute to the accumulating real-world paediatric safety dataset. From a health system perspective, the cost-effectiveness of CGRP-targeted therapies in the paediatric context has not yet been formally evaluated. Adult cost-effectiveness analyses have generally found anti-CGRP mAbs to be cost-effective for patients with high-frequency migraine and multiple prior preventive failures, but the substantially higher acquisition cost of biologic agents relative to generically available conventional drugs warrants consideration in paediatric formulary and payer negotiations [62]. The development of biosimilars for anti-CGRP mAbs, several of which are in clinical development as of 2025, may substantially improve access and cost-effectiveness over the coming years.

12. LIMITATIONS OF CURRENT EVIDENCE AND FUTURE RESEARCH DIRECTIONS

The current evidence base for pharmacological management of paediatric migraine is characterised by several significant limitations that constrain clinical practice and define urgent priorities for future investigation. These limitations span trial design, outcome measurement, patient population coverage, and long-term safety monitoring.

The paucity of large, well-powered RCTs in children under 12 years represents perhaps the most critical gap. The majority of paediatric migraine trials, including the CGRP-targeted therapy studies currently underway, focus predominantly on adolescents aged 12 to 17, whose physiological and pharmacokinetic characteristics more closely approximate adults. Evidence specifically applicable to children aged 6 to 11 years is largely absent for CGRP-targeted therapies and sparse even for conventional agents. Regulatory frameworks must provide stronger incentives for extending trial programmes to include younger age groups through paediatric study plans that explicitly address this evidence gap. The clinical and biological heterogeneity of paediatric migraine, encompassing episodic and chronic subtypes, presence or absence of aura, variable disability levels, and a wide developmental spectrum from early childhood to late adolescence, is inadequately captured by existing trial designs that typically pool diverse age groups and clinical presentations. Future trials should incorporate biomarker stratification, including CGRP plasma levels, neuroimaging-derived metrics, and genetic polygenic risk scores, to identify subpopulations most likely to benefit from specific pharmacological mechanisms, advancing the goals of precision medicine in paediatric headache care [63].

Outcome measurement in paediatric migraine trials requires standardisation and validation. Monthly migraine day reduction, borrowed from adult trial methodology, may not optimally capture the most clinically relevant outcomes for children, which include school attendance, cognitive function, sleep quality, and parent-reported disability, particularly in the younger age group where self-report reliability is limited. The development and psychometric validation of paediatric-specific outcome measures for migraine trials, including electronic patient-reported outcomes (ePROs) adaptable across developmental stages, represents a high-priority methodological research need. Long-term safety data for CGRP-targeted therapies in children represent a critical and urgent gap. CGRP plays important trophic and regulatory roles in the developing nervous system, cardiovascular system, and musculoskeletal system. The potential consequences of chronic CGRP pathway suppression during childhood, a period of profound biological plasticity, require systematic longitudinal evaluation through post-marketing registries, open-label extension studies, and pharmacoepidemiological surveillance. Mandatory paediatric safety monitoring plans for any approved CGRP-targeted therapy should incorporate bone mineral density surveillance, growth trajectory assessment, cardiovascular monitoring, and neurodevelopmental follow-up.

The potential for combining CGRP-targeted pharmacotherapy with validated non-pharmacological interventions in paediatric migraine has not been explored in controlled trials and represents a promising avenue for optimising treatment outcomes. Real-world effectiveness data from registry studies and electronic health record analyses will also be essential to complement RCT findings and provide generalisable evidence for routine clinical practice. Finally, pharmacogenomic predictors of response to CGRP-targeted therapies in children, including variants in CGRP pathway genes, tryptamine metabolism pathways, and blood-brain

barrier transporter genes, represent an underexplored frontier with the potential to personalise preventive therapy selection.

CONCLUSION

Paediatric migraine remains a condition of substantial unmet pharmacological need, characterised by a limited evidence base for preventive therapy, the landmark demonstration of conventional agent futility in the CHAMP trial, and a high burden of disability in a developmentally vulnerable population. The emergence of CGRP-targeted therapies, anti-CGRP monoclonal antibodies, and gepants offers a scientifically well-grounded and clinically promising advance, rooted in validated mechanistic understanding of migraine pathophysiology and supported by compelling adult trial evidence alongside early paediatric pharmacokinetic and safety data. Dedicated paediatric RCTs, including the REBUILD, SPACE, and HEADWAY trials, are positioned to provide the pivotal efficacy and safety evidence necessary for regulatory approval and integration into clinical practice.

Critical caution is warranted in applying adult efficacy data to children without paediatric-specific trial evidence, given the biological, pharmacokinetic, and methodological differences that fundamentally distinguish paediatric from adult migraine populations. The long-term safety implications of CGRP pathway suppression during child development, encompassing potential effects on bone mineral density, cardiovascular physiology, gastrointestinal function, and neurodevelopment, demand systematic prospective evaluation through adequately powered longitudinal studies and structured pharmacovigilance programmes. The paediatric migraine research community must prioritise inclusive trial designs spanning the full paediatric age spectrum, validated paediatric-specific outcome measures, and precision medicine approaches leveraging emerging biomarker and pharmacogenomic tools.

In the interim, clinical practice should integrate the best available evidence from conventional therapies within a shared decision-making framework that centres the child and family, incorporates non-pharmacological strategies, vigilantly monitors for adverse effects and medication overuse, and supports access to clinical trial participation where feasible. The ultimate goal of paediatric migraine pharmacotherapy, to interrupt the cycle of recurrent attacks, prevent the transition to chronicity, preserve neurodevelopmental trajectories, and restore quality of life, demands continued investment in rigorous, paediatric-specific clinical and translational research.

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