# What's new in migraine management in children and young people?

Ne-Ron Loh[1,2]; William P Whitehouse[3,4]; Rachel Howells[5]

[1]Paediatrics, Royal United Hospitals Bath NHS Foundation trust, Bath, UK;

[2]Paediatrics, Noah's Ark Children's Hospital, Cardiff, UK;

[3]School of Medicine, University of Nottingham, Nottingham, UK;

[4]Paediatric Neurology, Nottingham Children's Hospital, Nottingham University Hospital's NHS Trust, Nottingham, UK;

[5]Acute Paediatrics & Paediatric Neurology, Royal Devon& Exeter Hospital's NHS Foundation Trust, Exeter, UK

Corresponding author: Dr William P Whitehouse

Room EB2405

B Floor East Block

Queen's Medical Centre

Nottingham NG7 2UH

UK

william.whitehouse1@nottingham.ac.uk

telephone: 44 (0) 115 924 9924 ext 80692

fax: 44 (0) 115 970 9763

Key words: Adolescent Health, Neurology, Paediatrics, Pain, Therapeutics

This article has been accepted for publication in Archives of Disease in Childhood 2022 following peer review, and the Version of Record can be accessed online at http://dx.doi.org/10.1136/archdischild-2021-322373

Word count: 2,860

This article has been accepted for publication in Archives of Disease in Childhood 2022 following peer review, and the Version of Record can be accessed online at http://dx.doi.org/10.1136/archdischild-2021-322373

**Abstract**

For this narrative review we found recent publications on the use and effectiveness of old therapies including nutraceuticals, such as riboflavin, vitamin D, magnesium, melatonin, and talking therapies.

Recent large trials of established conventional pharmaceuticals such as propranolol, pizotifen, topiramate and amitriptyline for childhood migraine have failed, but the use of a quasi-placebo in future trials could help. We reviewed the evidence for angiotensin antagonists including candesartan in adults, but found a lack of evidence for their use in children.

There have been new developments in pharmaceuticals recently, including a more selective 5-HT1F agonist, lasmiditan, an effective acute treatment with no vasoconstrictor activity in adults, currently being tested in children. Also, a number of new Calcitonin Gene-Related Peptide (CGRP) antibodies and antagonists, with proven efficacy in acute treatment and or prevention of migraine in adults, are undergoing trials in children.

Peripheral nerve blocks and botulinum toxin are gaining popularity in adult practice, but we really need more good quality evidence for their effectiveness in children.

Finally, electroceuticals, that is therapeutic electric devices, are now marketed for acute and or preventative treatment, including an external trigeminal nerve stimulator

This article has been accepted for publication in Archives of Disease in Childhood 2022 following peer review, and the Version of Record can be accessed online at http://dx.doi.org/10.1136/archdischild-2021-322373

(e-TNS), a non-invasive vagal nerve stimulator (nVNS), a single-pulse transcranial magnetic stimulator (sTMS), and a remote electrical neuromodulation device (REN). At the moment, evidence for their effectiveness in children is still lacking.

So, there has been much progress, but mostly for adults. We are in urgent need of more migraine trials in children.

**Introduction**

The established management of migraine in children and young people starts with the clinical suspicion then diagnosis of migraine, followed by information and advice, including life-style changes, non-drug treatments, and shared decision making about medication. Much of this assessment, diagnosis, and treatment has not changed over the last 10 years. Previous reviews include articles in the Education and Practice supplement in 2013 and 2017.(1, 2) While NICE have reviewed their 2012 GC150 guideline for those aged over 12 years recently,(3) no substantial changes have been published as yet, and 2013 Quality Standards QS42 are still pertinent.(4) However, SIGN's 2018 evidence based guideline, includes some newer drug and device treatments.(5)

The pathophysiology of migraine is slowly becoming clearer, and the old concept of a "vascular headache" is misleading at best. However, why quite so many people are susceptible to this disorder of sensory processing with periodic incapacitating

This article has been accepted for publication in Archives of Disease in Childhood 2022 following peer review, and the Version of Record can be accessed online at http://dx.doi.org/10.1136/archdischild-2021-322373

headache with characteristic nausea, sleepiness etc still remains elusive.(6) Progress has also been made in understanding the genetic susceptibility.(7)

The paediatric concept of “periodic syndromes”, including infantile colic, benign paroxysmal torticollis, benign paroxysmal vertigo of childhood (not to be confused with benign positional vertigo), migraine, and cyclical vomiting has been revisited and reformulated as the “childhood migraine syndrome”(8)

Teaching and learning and support resources for health professionals are continuously updated and we recommend the Childhood Headache Training (CHaT) course and the headache module of the paediatric neurology Distance Learning Course, both organised by the British Paediatric Neurology Association.(9)

We will review the latest data on nutraceuticals and diet, and cognitive and behavioural therapies, however, the most exciting progress has been in the development of new drug treatments: pharmaceuticals, and devices: electroceuticals.

## Non-drug treatments

### Nutraceuticals

Potential complementary interventions in paediatric migraine include use of herbal remedies and nutraceuticals: compounds from foods which claim to have additional direct benefits on health. Complementary remedies are often used by paediatric

This article has been accepted for publication in Archives of Disease in Childhood 2022 following peer review, and the Version of Record can be accessed online at http://dx.doi.org/10.1136/archdischild-2021-322373

migraine patients at the time of referral to a headache clinic. Failure to confirm the effectiveness of conventional drug treatments in large randomised controlled trials (e.g. CHAMP, see below) has driven clinicians to search better-tolerated alternatives.

Studies of nutraceuticals in paediatric migraine have been of varying quality. However, recent findings suggest some may be worthy of attention (see table 1), given the small prospect of future large, high quality RCTs and the low risk of adverse effects. As there are no head-to-head data which demonstrate relative efficacy, our usual practice is to provide evidence-based information and suggest one, depending on patient preferences and attitudes as recommended by NICE for conventional migraine treatments.

**Riboflavin (Vitamin B2)**

NICE recommends advising adolescents and adults with migraine that Riboflavin 400mg may be effective at preventing attacks. An effective dose in children and young people may be lower, although RCTs have yielded conflicting results. Two recent studies which show faster time to pain freedom in migraine and / or reduced migraine frequency used riboflavin 50-400mg / day, in children as young as 6 years.(10) Riboflavin appears to be safe and well tolerated, with dose related darkening of urine and mild gastro-intestinal adverse effects reported in some.

This article has been accepted for publication in Archives of Disease in Childhood 2022 following peer review, and the Version of Record can be accessed online at http://dx.doi.org/10.1136/archdischild-2021-322373

## Vitamin D

Several studies report lower levels of vitamin D in adults and children with migraine than controls, and six months' vitamin D therapy can reduce symptom severity and migraine-related disability.(11) Also, children randomised to topiramate 2 mg/kg/day plus Vitamin D3 had fewer monthly migraines and migraine-related disability compared to those receiving topiramate alone.(12)

## Magnesium

Magnesium is well tolerated for adolescent migraine prevention although further RCTs are needed to determine optimum treatment regimens. Doses of up to 9 mg/kg/day of magnesium appear well tolerated. A meta-analysis of intravenous magnesium suggests efficacy in acute migraine in adults, but there is no high-quality evidence to recommend this or other intravenous abortive treatments in paediatric migraine at present.(13)

## Melatonin

Melatonin may exert a direct effect on migraine pathogenesis by inhibition of calcitonin gene-related peptide (CGRP) release and nitric oxide (NO) synthesis. A recent pilot study suggested that 4-8 mg was more effective acutely than 1-2 mg.(14) As for prevention, 0.3 mg/kg/day melatonin can reduce migraine frequency, severity,

This article has been accepted for publication in Archives of Disease in Childhood 2022 following peer review, and the Version of Record can be accessed online at http://dx.doi.org/10.1136/archdischild-2021-322373

and impact on quality of life.(15) However, melatonin was less effective than amitriptyline, in one recent RCT with a responder rate of 62% compared to 82%.(16) This is similar to the placebo responder rate of 60% in the CHAMP trial (see below).

There are no new data on other plant-based medicines, co-enzyme Q10, or nutraceutical combinations for paediatric migraine. We direct the reader to Rajapakse's (17) and Papetti's (18) recent reviews, which conclude that evidence for feverfew is mixed and insufficient for marijuana, St John's Wort and damask rose. Butterbur carries risks of hepatotoxicity and should not be recommended for migraine.

This article has been accepted for publication in Archives of Disease in Childhood 2022 following peer review, and the Version of Record can be accessed online at http://dx.doi.org/10.1136/archdischild-2021-322373

Table 1 Oral nutraceuticals: doses + evidence

| | **Dose & practical aspects** | **Evidence** |
|---|---|---|
| Riboflavin (vitamin B2) | 50-400 mg/day<br>Well tolerated, dark urine, and rare mild GI symptoms. | Shortened migraine attacks and reduced frequency in children as young as 6 years. |
| Vitamin D | 2 mg/kg/day<br>Well tolerated. | Reduced symptom severity and migraine-related disability. Children randomised to topiramate 2 mg/kg/day plus Vitamin D3 had fewer migraine attacks and less migraine-related disability compared to those on topiramate alone. |
| Magnesium | Up to 9 mg/kg/day as magnesium oxide<br>Well tolerated, rare mild diarrhoea. | More paediatric RCTs of oral prevention and acute intravenous treatment are needed. |
| Melatonin | 4 mg - 8 or mg or 0.3 mg/kg<br>Well tolerated, daytime sleepiness | For acute treatment, 4-8 mg was more effective than 1-2 mg. For prevention, 0.3 mg/kg/day can reduce migraine frequency and severity and improve quality of life. However, melatonin was less effective than amitriptyline: responder rate 62% compared to 82%. |

For references, please see the text.

## Topical treatments

Similarly, there is very little data on balms such as Tiger Balm®, 4-Head®, although chamomile (Matricaria chamomilla L) oleogel has recently been shown to reduce

This article has been accepted for publication in Archives of Disease in Childhood 2022 following peer review, and the Version of Record can be accessed online at http://dx.doi.org/10.1136/archdischild-2021-322373

migraine pain, recurrence, nausea, vomiting, photophobia and phonophobia more than placebo in a cross-over RCT in adults. Though not tested in paediatric migraine, topical chamomile has been shown to be efficacious and well tolerated for enuresis in children.

**Other dietary modifications**

The in-depth review by Papetti summarises the truths and myths about foods as trigger factors in paediatric migraine. There is no evidence that chocolate, other tyramine/phenylalanine containing foods, caffeine, alcohol, monosodium glutamate, aspartame or nitrites act as triggers for paediatric migraine.(18)

Evidence linking the ketogenic diet (KD) to remission or reduction in migraine frequency in adults goes back decades. In 2010 a study of a modified Atkins diet failed to show benefit in 8 adolescents with chronic daily headache. There is no evidence demonstrating the benefit of the KD in paediatric migraine.

**Obesity**

Many studies show a relationship between overweight / obesity and paediatric migraine, with low levels of physical activity in both obesity and migraine, and reduced migraine burden with weight loss. Tarantino and colleagues recently found a relationship between social and separation anxiety, migraine, and overweight in

This article has been accepted for publication in Archives of Disease in Childhood 2022 following peer review, and the Version of Record can be accessed online at http://dx.doi.org/10.1136/archdischild-2021-322373

children and adolescents.(19) They emphasised cognitive behavioural techniques to help children with migraine and improve children's self-esteem and coping ability.

## Sleep

There is a bi-directional relationship with sleep and migraine. Children with migraine are more likely than controls to have a range of sleep disorders, including difficulty falling asleep, less REM sleep, more arousals from sleep, obstructive sleep apnoea, and parasomnias**.**(20)

## Psychological interventions

Cognitive behavioural therapy (CBT) focuses on developing coping strategies with migraine-related disability and comorbid symptoms such as anxiety and depression. It may include psychoeducation on the gate theory of pain and training in techniques such as diaphragmatic breathing or progressive muscle relaxation, guided imagery, distraction and problem-solving. Other psychological therapies include biofeedback training and mindfulness meditation.

A recent meta-analysis of 14 studies of CBT in paediatric migraine showed reduced headaches both immediately and three months after intervention (pooled odds ratios of 9 for each).(21) In young people with chronic migraine, 5 months' CBT with amitriptyline was superior to amitriptyline with headache education, with sustained

This article has been accepted for publication in Archives of Disease in Childhood 2022 following peer review, and the Version of Record can be accessed online at http://dx.doi.org/10.1136/archdischild-2021-322373

improvement for at least a year.(22) Many studies of headaches and other pain disorders in children and adolescents have confirmed that remote CBT can reduce headache severity, independent of improvements in anxiety or depression.(23) In a meta-analysis of ten adult RCTs mindfulness meditation improved pain intensity and headache frequency, (24) and in adolescents with chronic pain, including 7 with headache, group-based mindfulness interventions reduced functional disability and frequency of pain.(25) There are no new data for biofeedback training in paediatric migraine.

**Established pharmaceuticals**

There remains a lack of good evidence for commonly used migraine treatments, especially in children. Unfortunately an ambitious RCT (P3MC) of pizotifen and propranolol (popular preventative treatments in the UK) was abandoned by the Health Technology Assessment (HTA) government funding body because of delays and slow recruitment.(26) More recently a large RCT (CHAMP) of topiramate and amitriptyline (popular preventative treatments in the USA), was abandoned because interim-analyses showed a prohibitively high placebo responder rate (61%).(27)

The problem of high placebo responder rates has been recognised in some, but not all migraine trials, and may be more likely with children, and with broader inclusion criteria. One innovative, theoretical strategy is to use a quasi-placebo, e.g. riboflavin or melatonin as a comparator in place of a traditional placebo.(28) If the

This article has been accepted for publication in Archives of Disease in Childhood 2022 following peer review, and the Version of Record can be accessed online at http://dx.doi.org/10.1136/archdischild-2021-322373

investigational medicinal product (IMP) is not found to be superior, e.g. if the quasi-placebo had a high responder rate of 60%, then at least it could be rationally used as a therapy. Conventional placebos cannot be used like this.

Trials of flunarizine, valproate, gabapentin, cyproheptadine, pizotifen are either old, under-powered, or unlikely to be funded in children.

**Angiotensin antagonists**

Drugs which act on the Renin Angiotensin System, such as candesartan, an angiotensin II -receptor A1 blocker (ARB), have been in use in adult migraine for a decade, seem as effective as propranolol (29) and are supported by the recent SIGN evidence-based guideline. Lisinopril, an Angiotensin Converting Enzyme (ACE) inhibitor, decreases the formation of active angiotensin II from angiotensin I, and so is also likely to be an effective treatment. It seems worth pursuing paediatric migraine trials with this group of drugs.

**Serotonin agonists**

A whole panoply of triptans, 5-hydroxytryptamine agonists (5-HT 1B/1D), have been shown to be effective acute migraine treatments, in children as well as adults.(30) More selective serotonin agonists “ditans” have been developed, e.g. Lasmiditan, a 5-HT 1F agonist, effective in adults where it affords a theoretical safety advantage. Trials in children are under way: PIONEER PEDS- 1 and PEDS-2.

This article has been accepted for publication in Archives of Disease in Childhood 2022 following peer review, and the Version of Record can be accessed online at http://dx.doi.org/10.1136/archdischild-2021-322373

**Calcitonin Gene-Related Peptide (CGRP) antibodies and antagonists**

In the last few years monoclonal antibodies against CGRP and its receptor, and CGRP-receptor antagonists, known as ”GPANTS” have been developed and shown effective in adults with migraine, as acute treatments and preventatives. (31, 32) CGRP is intimately involved in the pathophysiology of a migraine attacks. Its release from the brain as a pain signal activates a host of effects including vasodilatation, and other inflammatory responses. Injecting people with migraine with synthetic CGRP triggers a typical migraine attack. Currently a number are in paediatric clinical trials (tables 2, and 3).

Table 2. CGRP monoclonal antibodies for migraine

| CGRP monoclonal antibody | Erenumab (*Aimovig*) | Fremanazumab (*Ajovy*) | Galcanezumab (*Emgality*) | Eptinezumab (*Vyepti*) |
|---|---|---|---|---|
| Indication | Prevention | Prevention | Prevention | Prevention |
| Target | CGRP receptor | CGRP | CGRP | CGRP |
| Administration | Subcutaneous | Subcutaneous | Subcutaneous | Intravenous |
| Frequency | monthly | 3 monthly | monthly | 3 monthly |
| Percentage with > 50% reduction in headache days Responder rate | 50% (27% with placebo) 1 | 41% (18% with placebo) 2 | 27% (15% with placebo) 3 | 61% (39% with placebo) 4 |
| Paediatric trials | OASIS (CM) (EM) | | REBUILD-1 | PROSPECT 2 |

Table 3. CGRP antagonists: GPANTS for migraine

| CGRP antagonist | Rimegepant (*Nurtec*) | Ubrogepant (*Ubrelvy*) | Atogepant | Vazegepant aka Zavegepant |
|---|---|---|---|---|

This article has been accepted for publication in Archives of Disease in Childhood 2022 following peer review, and the Version of Record can be accessed online at http://dx.doi.org/10.1136/archdischild-2021-322373

| Current indication | Acute treatment and prevention | Acute treatment | Prevention | Acute treatment and prevention |
|---|---|---|---|---|
| Formulation | tablet | tablet | tablet | nasal spray and tablet |
| Regime | Up to once a day | Up to twice a day | Undergoing phase 3 trials | Undergoing phase 3 trials |
| 2- hour pain free | 20% (placebo 12%) | 21% (placebo 11%) | | 23% (placebo 15%) |
| 2-hour pain relief | 58% (placebo 42%) [1] | 61% (placebo 48%) [2] | | |
| Paediatric trials | NCT04649242 NCT04743141 | deferred 2019 | deferred 2019 | |

**Neuromodulation**

There are many patients who are not adequately treated with currently available medications, or who have contraindications or adverse effects. Also, some patients prefer for non-drug options.

Neuromodulation is a rapidly expanding area of research and development. It is defined by the International Neuromodulation Society as the “alteration or modulation of nerve activity by delivering electrical or pharmaceutical agents directly to a target area”.

**Peripheral Nerve blocks**

Although peripheral nerve blocks have been in regular use in adult headache clinics for decades, the evidence base is still variable. In the paediatric age group there are numerous case series but no RCTs.(33) They are safe and well tolerated procedures

This article has been accepted for publication in Archives of Disease in Childhood 2022 following peer review, and the Version of Record can be accessed online at http://dx.doi.org/10.1136/archdischild-2021-322373

undertaken in a clinic setting. They can provide rapid pain relief within minutes for migraine, allodynia, medication overuse headache, and cluster headache, as well as for surgical procedures. The effects can last from weeks to months, outlasting the expected pharmacological action of the anaesthetic at the injection site. In experimental studies a single greater occipital nerve block was associated with changes to auditory evoked potentials a week later, which was predictive of transforming chronic to episodic migraine.(34)

Most studies use a local anaesthetic agent plus a corticosteroid injected around the target nerve resulting in anaesthesia of the nerves distribution. Lidocaine, bupivacaine, and methylprednisolone or triamcinolone are popular choices. Adult studies suggest similar efficacy with or without steroids. We personally use lidocaine alone in children as young as 8 years. We avoid steroid components, as these have been implicated in fat atrophy and hair loss at the injection site. The most common sites are superficial and accessible: the greater, and lesser occipital nerves, supraorbital, and supatrochlear nerves, and, less commonly, auriculotemporal nerves and the sphenopalatine ganglion (see figure 1). These all have second order neuron convergence with the trigemino-cervical plexus involved in migraine propagation. The sphenopalatine ganglion is a set of neurons located in the ptergopalatine fossa that contain sensory nerves to V2 distribution as well as sympathetic and parasympathetic nerves. Some adult catheters facilitate placement of the anaesthetic in the nostril, but these catheters are less suitable for smaller children, in whom an 8-French nasogastric tube works well.

This article has been accepted for publication in Archives of Disease in Childhood 2022 following peer review, and the Version of Record can be accessed online at http://dx.doi.org/10.1136/archdischild-2021-322373

## Botulinum toxin A

Botulinum toxin has been used in paediatrics for the management of spasticity and in adults achieved marketing authorisation for chronic migraine after the PREEMPT-1 and -2 RCTs. However, a paediatric RCT did not demonstrate efficacy (35), although several case series did.(36) Typically, 5 units of botulinum toxin is injected at each of 31 sites, based on the original protocol for PREEMPT. Each injection stings for several seconds, so may not be tolerated in younger children, unlike nerve blocks where local anaesthetics numbs the site. Having nitrous oxide on hand would be helpful as the whole procedure can take around 15 minutes to complete.

## Acupuncture

Acupuncture is a form of Chinese traditional medicine that involves inserting fine needles into various traditionally mapped points of the body. It was recommended in NICE CG150 as a treatment option for chronic tension-type headache and migraine.(3) More recently, a Cochrane systematic review has recommended acupuncture as an adjunct treatment for migraine headaches,(37) but there have only been a few small paediatric studies. However, it appears safe and may be effective as an acute, as well as preventative treatment in children.(38)

## Electroceuticals

See the Migraine Trust for patient information on some of these devices, and table 4.

Although we have described some of the devices currently marketed, there is little

This article has been accepted for publication in Archives of Disease in Childhood 2022 following peer review, and the Version of Record can be accessed online at http://dx.doi.org/10.1136/archdischild-2021-322373

evidence to support their use in children and young people. Their use, at the moment, in children is unproven, and we recognise there is an urgent need for clinical trials of electroceuticals in children.

**External Trigeminal Nerve Stimulator (e-TNS)**

*Cefaly*® is a propriety e-TNS. It comprises a magnetised electrode strip adhered to the forehead. On activation it stimulates supratrochlear and supraorbital branches of the ophthalmic nerve (V1). It can feel like “a pinching rubber band”. Topical local anaesthetic cream can be used at the site for the first few days, and it takes 2 days to 2 weeks for patients to tolerate the whole programme: 20 minutes on, and repeated, if needed, after 60 minutes off, several times a day. This device can be purchased over the counter with a “money back” arrangement. An RCT (PREMICE) trial compared therapeutic stimulation with ~~a~~ sham frequency stimulation in 67 adults. The 50% responder rate was 38%, versus 12% for sham stimulation (P = 0.023). In the authors’ experience, the device can be safely used in children, however tolerability is an issue for some.(39)

**Non-invasive Vagal Nerve Stimulator (nVNS)**

*GammaCore*® is a proprietary nVNS. In an RCT of 243 adults with episodic migraine (PRESTO), 12% were pain free at 30 minutes versus 4% with sham stimulation (P =0 .01), and 21% were pain free at 60 minutes versus 10% with sham stimulation (P =0 .02).(40) The device is placed near the vagal nerve on either side of the

This article has been accepted for publication in Archives of Disease in Childhood 2022 following peer review, and the Version of Record can be accessed online at http://dx.doi.org/10.1136/archdischild-2021-322373

patient's neck. The programme stimulates the vagal nerve for 2 minutes up to 15 times a day. It can feel like a numbing vibration and sometimes causes muscle twitches on the neck and face.

**Single-pulse Transcranial Magnetic Simulator (sTMS)**

*TMS mini*™ is a proprietary device for delivering sTMS. In an RCT of 164 adults with migraine with aura 39% were pain free at 2 hours versus 22% with sham treatment.(41) STMS is applied to the occiput and most patients cannot feel the pulses. Occasionally there is a tingling or ringing in the ears. For acute treatment 3 pulses are delivered, which can be repeated. For preventative treatment, 4 pulses are delivered twice a day. It has marketing authorisation for acute and preventative migraine treatment in adults. It weighs nearly 2 kg and needs to be carried in a backpack or large handbag. It is currently not available in the UK.

**Remote electrical neuromodulation (REN) device**

Nerivio® is a proprietary REN device. It is a wireless device worn on the patient's arm and controlled by a smart-phone app for the acute treatment of migraine. The device generates a signal in pain sensory fibres peripherally in the arm that is thought to induce pain modulation. It causes a mild tingling sensation. In an RCT of 252 adults with episodic migraine, 37% were pain free at 2 hours compared to 18% with sham treatment.(42) In an open label study of 39 12-17-year olds, 71%

This article has been accepted for publication in Archives of Disease in Childhood 2022 following peer review, and the Version of Record can be accessed online at http://dx.doi.org/10.1136/archdischild-2021-322373

responded, including 35% who were pain free, and at 2 hours.(43) It is FDA approved in the USA for migraine treatment from age 12 years old but is not yet available in the UK.

This article has been accepted for publication in Archives of Disease in Childhood 2022 following peer review, and the Version of Record can be accessed online at http://dx.doi.org/10.1136/archdischild-2021-322373

Table 4. Current electroceuticals for migraine

| Device | e-TNS | nVNS | sTMS | REN |
|---|---|---|---|---|
| Example | *Cefaly*® | *gammaCore*® | *sTMS mini*™ | *Nerivio*® |
| Age marketing authorised (years) | > 8 | > 12 (in USA) | > 12 | > 12 |
| Mechanism of action | Trigeminal nerve stimulation | Suppresses glutamate in trigeminal nucleus | Increases threshold of occipital cortex | Induced peripheral pain modulation |
| Method of application | Electrode placed on forehead | Placed on neck near vagus nerve | Placed on occiput | Attached to arm and controlled by an app |
| Acute treatment 2-hour pain free | 17% (sham 7%) | 30% (sham 20%) | 39% (sham 22%) | 37% (sham 18%) |
| Acute treatment 2-hour pain relief | 65% (sham 52%) | 41% (sham 28%) | N/A | 67% (39% sham) |
| Preventative treatment Responder rate | 38% had > 50% decrease in migraine attacks (sham 12%) | 31% had > 50% decrease in migraine days (sham 25%) | 46% had > 50% decrease in headache days | N/A |

e-TNS= external trigeminal nerve stimulation; nVNS= non-invasive vagus nerve stimulation; REN= remote electrical neuromodulation; sTMS = single pulse transcranial magnetic stimulation; USA= United States of America.

For references, please see text.

## Conclusions

As expected, new developments in therapy have been pioneered in adults with migraine. However, there is new evidence for the role of psychological support and CBT. The “failure” of the CHAMP trial speaks to the success of the placebo effect in

This article has been accepted for publication in Archives of Disease in Childhood 2022 following peer review, and the Version of Record can be accessed online at http://dx.doi.org/10.1136/archdischild-2021-322373

that trial which will include the contact, attention, support, and validation given to all trial participants. Designing trials with a quasi-placebo (28) e.g. as in the melatonin *vs* amitriptyline trial (16) would allow such trials to still yield useful results. Even so evidence of new effective acute and preventative treatments is emerging for adults with migraine, including angiotensin antagonists, CGRP antibodies and antagonists, injections, and devices. So, we wait with interest for the results of the current wave of paediatric RCTs. In the meantime we offer a management approach that uses available evidence and respected guidance first backed up by discussion around alternative treatments and where we are with evidence for these – see flowchart 1.

This article has been accepted for publication in Archives of Disease in Childhood 2022 following peer review, and the Version of Record can be accessed online at http://dx.doi.org/10.1136/archdischild-2021-322373

## References

1. McCrea N, Howells R. 15-minute consultation: headache in children under 5 years old. *Arch Dis Child Educ Pract Ed* 2013;98:181-185. doi:10.1136/archdischild-2012-303529.

2. Whitehouse WP, Agrawal AS. Management of children and young people with headache. *Arch Dis Child Educ Pract Ed* 2017;102:58–65. doi:10.1136/archdischild-2016-3.

3. ttps://www.nice.org.uk/guidance/cg150/chapter/Recommendations#management-2 (accessed 14-10-2021).

4. https://www.nice.org.uk/guidance/qs42/resources/headaches-in-over-12s-pdf-2098663350469 (accessed 14-10-2021).

5. Scottish Intercollegiate Guidelines Network (SIGN). Pharmacological management of migraine. Edinburgh: SIGN; 2018. (SIGN publication no. 155). [February 2018]. Available from URL: http://www.sign.ac.uk (accessed 29-10-2021).

6. Qubty W, Patniyot I. Migraine pathophysiology. *Pediatr Neurol* 2020;107:1e63. https://doi.org/10.1016/j.pediatrneurol.2019.12.014 .

7. de Boer I, van den Maagdenberg AMJM, Terwindt GM. Advance in genetics of migraine. *Curr Opin Neurol* 2019;32:413–421. doi:10.1097/WCO.0000000000000687.

8. Abu-Arafeh I, Gelfand AA. The childhood migraine syndrome. *Nat Rev Neurol* 2021;17:449–458. https://doi.org/10.1038/s41582-021-00497-6.

This article has been accepted for publication in Archives of Disease in Childhood 2022 following peer review, and the Version of Record can be accessed online at http://dx.doi.org/10.1136/archdischild-2021-322373

9. https://courses.bpna.org.uk/ (accessed 14-10-2021).

10. Yamanaka G, Suzuki S, Takeshita M. Effectiveness of low-dose riboflavin as a prophylactic agent in pediatric migraine. Brain Dev 2020;42(7):23-528.

11. Donmez A, Orun E, Sonmez F. Vitamin D status in childhood headache: a case-control study. *Clin Nutr Espen* 2018;23:222-227.

12. Fallah R, Yahd S, Sohrevardi S. Efficacy of Topiramate alone and Topiramate plus Vitamin D3 in the prophylaxis of pediatric migraine: A randomized clinical trial. *Iran J Child Neurol* 2020;14(4):77-86.

13. Werner K, Qaiser S, Kabbouche M at al. Intravenous migraine treatment in children and adolescents. *Curr Pain Headache Rep* 2020;24(9):54.

14. Gelfand A, Ross A, Irwin S. Melatonin for acute migraine treatment in children and adolescents: a pilot randomized trial. *Headache* 2020;60(8):1712-1721.

15. Fallah R, Shoroki FF, Ferdosian F. Safety and efficacy of Melatonin in pediatric migraine prophylaxis. Curr Drug Saf 2015;10(2):132-5. doi: 10.2174/1574886309666140605114614

16. Fallah R, Fazelishoroki F, Sekhavat L. A randomised clinical trial of efficacy of melatonin and amitriptyline in migraine prophylaxis of children. Iran J Child Neurol 2018;12:47-54.

17. Rajapakse T, Davenport WJ. Phytomedicines in the treatment of migraine. *CNS Drugs* 2019;33(5):399-415. doi: 10.1007/s40263-018-0597-2

This article has been accepted for publication in Archives of Disease in Childhood 2022 following peer review, and the Version of Record can be accessed online at http://dx.doi.org/10.1136/archdischild-2021-322373

18. Papetti L, Moavero R, Ferilli MAN. Truths and myths in pediatric migraine and nutrition. *Nutrients* 2021;13(8):2714. doi: 10.3390/nu13082714

19. Tarantino S, Papetti L, Di Stefano A, et al. Anxiety, Depression, and Body Weight in Children and Adolescents with Migraine. *Front Psychol* 2020;11:911.. doi:10.3389/fpsyg.2020.530911.

20. Pavkovic IM, Kothare SV. Migraine and sleep in children: a bidirectional relationship. *Pediatr Neurol* 2020;109:20-27. DOI:10.1016/j.pediatrneurol.2019.12.013.

21. Ng QX, Venkatanarayanan N, Kumar L. A systematic review and meta-analysis of the efficacy of cognitive behavioural therapy for the management of paediatric migraine. *Headache* 2017;57(3):349-362. doi: 10.1111/head.13016.

22. Kroner JW, Peugh J, Kashikar-Zuck SM, et al. Trajectory of improvement in children and adolescents with chronic migraine: results from the cognitive behavioural therapy and amitriptyline trial. *J Pain* 2017;18(6):637-644. Doi: 10.1016/j.jpain.2017.01.002.

23. Fisher E, Law E, Dudeney J, et al. Psychological therapies (remotely delivered) for the management of chronic and recurrent pain in children and adolescents. *Cochrane Data Syst Rev* 2019;Apr2;4(4). doi:10.1002/14651858.CD011118.pub3.

24. Gu Q, Hou J-C, Fang X-M. Mindfulness Meditation for primary headache pain: a meta-analysis. *Chin Med J* 2018;131(7):829-838. DOI: 10.4103/0366-6999.228242.

This article has been accepted for publication in Archives of Disease in Childhood 2022 following peer review, and the Version of Record can be accessed online at http://dx.doi.org/10.1136/archdischild-2021-322373

25. Waelde LC, Feinstein AB, Bhandari R, et al. A pilot study of mindfulness meditation for pediatric chronic pain. *Children* 2017;4:32. Doi: 10.3390/children4050032.

26. Silcocks P, Whitham D, Whitehouse WP. P3MC: a double-blind parallel group randomised placebo-controlled trial of Propranolol and Pizotifen in preventing migraine in children. *Trials* 2010;11:71. doi: 10.1186/1745-6215-11-71.

27. Powers SW, Coffey CS, Chamberlin LA, et al. Trial of Amitriptyline, Topiramate, and Placebo for Pediatric Migraine. *N Engl J Med* 2017;376:115-124. DOI: 10.1056/NEJMoa1610384].

28. Whitehouse WP. A quasi-placebo may have a role in some randomised controlled trials. *Trials* 2018:19:92 DOI 10.1186/s13063-018-2496-8).

29. Stovner LJ, Linde M, Gravdahl GB, et al. A comparative study of candesartan versus propranolol for migraine prophylaxis: A randomised, triple-blind, placebo-controlled, double cross-over study. *Cephalalgia* 2014;34:523–532. DOI: 10.1177/0333102413515348].

30. Richer L, Billinghurst L, Linsdell MA, et al. Drugs for the acute treatment of migraine in children and adolescents. Cochrane Database Syst Rev. 2016;4:CD005220.

31. Edvinsson L. CGRP receptor antagonists and antibodies against CGRP and its receptor in migraine treatment. *Br J Clin Pharmacol* 2015;80:193–199. DOI:10.1111/bcp.12618.

This article has been accepted for publication in Archives of Disease in Childhood 2022 following peer review, and the Version of Record can be accessed online at http://dx.doi.org/10.1136/archdischild-2021-322373

32. Pellesi L, Guerzoni S, Pini LA. Spotlight on Anti-CGRP monoclonal antibodies in migraine: the clinical evidence to date. *Clin Pharmacol Drug Dev* 2017;6:534–547.

33. Pulleda F, Goadsby PJ, Prabhakar P. Treatment of disabling headache with greater occipital nerve injections in a large population of childhood and adolescent patients: a service evaluation. *J Headache Pain* 2018;19:5. DOI 10.1186/s10194-018-0835-5.

34. Viganò A, Torrieri MC, Toscano M, et al. Neurophysiological correlates of clinical improvement after greater occipital nerve (GON) block in chronic migraine: relevance for chronic migraine pathophysiology. *J Headache Pain*. 2018;19(1):73.

35. Winner PK, Kabbouche M, Yonker M, et al. A randomized trial to evaluate OnabotulinumtoxinA for prevention of headaches in adolescents with chronic migraine. *Headache* 2020;60:564-575.

36. Marcelo R, Freund B. The Efficacy of Botulinum Toxin in Pediatric Chronic Migraine: A Literature Review. *J Child Neurol* 2020;35(12):844-851. doi:10.1177/0883073820931256. Epub 2020 Jun 24. PMID: 32580690.

37. Linde K, Allais G, Brinkhaus B, et al. Acupuncture for the prevention of episodic migraine. Cochrane Database of Systematic Reviews 2016, Issue 6. Art. No.: CD001218. DOI: 10.1002/14651858.CD001218.pub3.

38. Graff DM, McDonald MJ. Auricular Acupuncture for the Treatment of Pediatric Migraines in the Emergency Department. Pediatr Emerg Care. 2018;34(4):258-262. doi: 10.1097/PEC.0000000000000789.

This article has been accepted for publication in Archives of Disease in Childhood 2022 following peer review, and the Version of Record can be accessed online at http://dx.doi.org/10.1136/archdischild-2021-322373

39. Schoenen J, Vandersmissen B, Jeangette S, et al. Migraine prevention with a supraorbital transcutaneous stimulator: A randomized controlled trial. Neurology 2013;80. doi.org/10.1212/WNL.0b013e3182825055).

40. Tassorelli C, Grazzi L, de Tommaso M, et al. Noninvasive vagus nerve stimulation as acute therapy for migraine: The randomized PRESTO study. Neurology 2018;91:e364-e373. doi:10.1212/WNL.0000000000005857.

41. Lipton RB, Dodick DW, Silberstein SD, et al. Single-pulse transcranial magnetic stimulation for acute treatment of migraine with aura: a randomized, double-blind, parallel-group, sham-controlled trial. Lancet Neurol 2010;9(4):373-80.

42. Yarnitsky D, Dodick DW, Grosber, BM, et al. Remote Electrical Neuromodulation (REN) Relieves Acute Migraine: A Randomized, Double-Blind, Placebo-Controlled, Multicentre Trial. Headache 2019;59:240-1252. https://doi.org/10.1111/head.13551.

43. Hershey AD, Lin T, Gruper Y, Harris D, et al. Remote electrical neuromodulation for acute treatment of migraine in adolescents. Headache 2021;61(2):310-317. doi: 10.1111/head.14042. Epub 2020 Dec 21. PMID: 3334992.

**References for table 2**

1. Tepper S, Ashina M, Reuter U, et al. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. *Lancet Neurol* 2017;16(6):425-434. doi: 10.1016/S1474-4422(17)30083-2. Epub 2017 Apr 28. PMID: 28460892.

This article has been accepted for publication in Archives of Disease in Childhood 2022 following peer review, and the Version of Record can be accessed online at http://dx.doi.org/10.1136/archdischild-2021-322373

2. Silberstein SD, Dodick DW, Bigal ME, et al. Fremanezumab for the Preventive Treatment of Chronic Migraine. *N Engl J Med* 2017;377(22):2113-2122. doi: 10.1056/NEJMoa1709038. PMID: 29171818.

3. Detke HC, Goadsby PJ, Wang S, et al. Galcanezumab in chronic migraine: The randomized, double-blind, placebo-controlled REGAIN study. *Neurology* 2018;91(24):e2211-e2221. doi: 10.1212/WNL.0000000000006640. Epub 2018 Nov 16. PMID: 30446596; PMCID: PMC6329331.

4. Lipton RB, Goadsby PJ, Smith J, et al. Efficacy and safety of eptinezumab in patients with chronic migraine: PROMISE-2. *Neurology* 2020;94(13):e1365-e1377. doi:10.1212/WNL.0000000000009169

**References for table 3**

1. Lipton RB, Croop R, Stock EG, et al. Rimegepant, an Oral Calcitonin Gene Related Peptide Receptor Antagonist for Migraine. *N Engl J Med* 2019;381:142-149. DOI: 10.1056/NEJMoa1811090.

2. Dodick DW, Lipton RB, Ailani J, et al. Ubrogepant for the Treatment of Migraine. *N Engl J Med* 2019;381(23):2230–41. https://doi.org/10.1056/NEJMoa1813049. 2020 Dec 21. PMID: 3334992.

This article has been accepted for publication in Archives of Disease in Childhood 2022 following peer review, and the Version of Record can be accessed online at http://dx.doi.org/10.1136/archdischild-2021-322373

What is known about this topic

- There is little evidence to support drug treatments for migraine in children and young people.
- Some new treatments have become available for adults with migraine.

What this study adds

- An up-to-date narrative review of the accumulating evidence for nutraceuticals and talking therapies in childhood migraine.
- How problems caused by a high placebo response rate in paediatric drug trials might be addressed.
- A review of novel pharmaceuticals particularly CGRP antibodies and antagonists, and ditans, currently in paediatric trials.
- A description of some new electroceuticals marketed for adult migraine.

So what?

- Migraine is so common that all general and specialist paediatricians seeing school age children and young people will come across it and be asked for advice.
- We hope this review will help paediatricians discuss the wide range of new treatments for adults, which hopefully will soon be available for children, including electroceuticals as well as pharmaceuticals.

This article has been accepted for publication in Archives of Disease in Childhood 2022 following peer review, and the Version of Record can be accessed online at http://dx.doi.org/10.1136/archdischild-2021-322373

- This review will also help discussions about nutraceutical therapies, and support demands for better access to talking therapies e.g. CBT.

**Flowchart: Child / young person with migraine**

**Explanation**

- Deal with patient + parent/carers' ideas, concerns (e.g. fear of secondary headache) and expectations (e.g. of a cure).
- Make a positive diagnosis of migraine.
- Signpost support, e.g. MigraineTrust.

**Management**

- Acute attacks and prevention

Acute attacks

- Analgesia: NSAID and or paracetamol, combined with triptan as early as possible during an attack*
- Rest / sleep as needed
- Topical remedies as adjunct e.g. 4head, Tiger Balm
- Add an antiemetic if above ineffective, even if not vomiting
- Explain how to avoid Medication Overuse Headache*

*NICE Quality Standard 42 for young people and adults over 12 years of age.

(continues on next page)

This article has been accepted for publication in Archives of Disease in Childhood 2022 following peer review, and the Version of Record can be accessed online at http://dx.doi.org/10.1136/archdischild-2021-322373

Acute attacks: next steps

- If patient wishes to explore other topical remedies discuss Chamomile oleogel, taking into account limited evidence of benefit in children
- Discuss that lasmiditan may be a proven alternative to triptans in the future
- Discuss that GPANTS may be proven alternatives in the future
- Discuss neuromodulators for acute treatment of migraine, stressing lack of evidence in children at present.

Prevention

- Identify triggers and explore ways to mitigate them
- Stress importance of regular and adequate sleep, exercise, meals, hydration
- Pay attention to psychosocial vulnerabilities and signpost to resources e.g. counselling at school / college, self-help websites / apps e.g. YoungMinds, Kooth, Headspace, and where available, refer for CBT
- Discuss impact of exercise / obesity on migraine.

- Discuss the benefits and risks of prevention medication, taking into account their preferences, co-morbidities, risk of adverse effects, and the impact of headache on quality of life. Discuss NICE recommended treatments e.g. topiramate, amitriptyline, propranolol, taking into account risks and adverse effects with each.

- Discuss riboflavin: a dose below 400mg / day may be effective.

Prevention: next steps

Review the diagnosis, including use of headache diary.

- If patient prefers to explore nutraceuticals discuss riboflavin, magnesium, melatonin, or vitamin D, and the limited evidence of benefit in children
- Discuss acupuncture
- Discuss candesartan, CGRP antibodies and GPANTS, and other agents likely to be available for children in the future
- If treatment failure with the above, discuss injectable treatments and the limited evidence in children, and as required
- Discuss neuromodulators for acute treatment of migraine, stressing lack of evidence in

This article has been accepted for publication in Archives of Disease in Childhood 2022 following peer review, and the Version of Record can be accessed online at http://dx.doi.org/10.1136/archdischild-2021-322373

This article has been accepted for publication in Archives of Disease in Childhood 2022 following peer review, and the Version of Record can be accessed online at http://dx.doi.org/10.1136/archdischild-2021-322373