Migraine headache in children

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ABSTRACT

INTRODUCTION: Diagnosis of migraine headache in children can be difficult as it depends on subjective symptoms; diagnostic criteria are broader than in adults. Migraine occurs in 3% to 10% of children and increases with age up to puberty. Migraine spontaneously remits after puberty in half of children, but if it begins during adolescence it may be more likely to persist throughout adulthood. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical question: What are the effects of treatments for acute attacks, and of prophylaxis for migraine headache in children? We searched: Medline, Embase, The Cochrane Library, and other important databases up to June 2010 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 22 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: for acute symptom relief (antiemetics, codeine phosphate, non-steroidal anti-inflammatory drugs [NSAIDs], paracetamol, and 5HT1 antagonists [such as triptans]) and for prophylaxis (beta-blockers, dietary manipulation, pizotifen, progressive muscle relaxation, stress management, thermal biofeedback, and topiramate).

QUESTIONS

INTERVENTIONS

Key points

- Diagnosis of migraine headache in children can be difficult as it depends on subjective symptoms; diagnostic criteria are broader than in adults.

  Migraine occurs in 3% to 10% of children and increases with age up to puberty.

  Migraine spontaneously remits after puberty in half of children, but if it begins during adolescence, it may be more likely to persist throughout adulthood.

- We don't know whether paracetamol, NSAIDs, or codeine phosphate relieve the pain of migraine in children, as we found few good trials. Nevertheless, it is widely accepted good clinical practice that paracetamol, an NSAID such as ibuprofen, or both, should be the first-line agents for headache relief during acute attacks unless contraindicated.

- There is increasing RCT evidence that nasal sumatriptan is likely to be beneficial in reducing pain at 2 hours in children aged 12 to 17 years with persisting headache.

  We found limited evidence that oral almotriptan may be more effective than placebo at reducing pain at 2 hours, but not at reducing recurrence.

  Oral rizatriptan may reduce nausea but it has not been shown to reduce pain compared with placebo.

We don't know whether oral zolmitriptan or eletriptan are effective; data regarding zolmitriptan are conflicting and data regarding eletriptan are limited.

- We don't know whether antiemetics are beneficial for treating acute attack of childhood migraine, as we found no trials.
- Pizotifen is widely used as prophylaxis in children with migraine, but we found no trials assessing its efficacy.

When used prophylactically, stress management programmes may improve headache severity and frequency in the short term compared with no stress management.

Trials of beta-blockers as prophylaxis in children have given inconsistent results, and propranolol may even increase the duration of headaches compared with placebo.

We don't know whether prophylactic dietary manipulation, thermal biofeedback, or progressive muscle relaxation can prevent recurrence of migraine in children.

- There is some inconclusive RCT evidence that topiramate may be useful as prophylaxis in children with migraine.

Clinical context

DEFINITION

Migraine is defined by the International Headache Society (IHS) as a recurrent headache that occurs with or without aura and that lasts 2 to 48 hours. [1] It is usually unilateral in nature, pulsating in quality, of moderate or severe intensity, and is aggravated by routine physical activity. Nausea, vomiting, photophobia, and phonophobia are common accompanying symptoms. This review focuses on migraine in children <18 years of age. Diagnostic criteria for children are broader than criteria for adults, allowing for a broader range of duration and a broader localisation of the pain (see table 1, p 29). [2] Diagnosis is difficult in young children as the condition is defined by subjective symptoms. Studies that do not explicitly use criteria that are congruent with IHS diagnostic criteria (or revised IHS criteria in children <16 years of age) have been excluded from this review. Many children with a symptom cluster that includes headache may not perfectly match the IHS classification, but may benefit from medical interventions currently in use. A liberal approach to symptomatology is therefore likely to be beneficial in clinical practice.

INCIDENCE/ PREVALENCE

Migraine occurs in 3% to 10% of children, [3] [4] [5] [6] [7] and currently affects 50/1000 school-age children in the UK and an estimated 7.8 million children in the European Union. [8] Studies in resource-poor countries suggest that migraine is the most common diagnosis among children presenting with headache to a medical practitioner. It is rarely diagnosed in children <2 years of age because of the symptom-based definition, but it increases steadily with age thereafter. [1] [9] [10] Migraine affects boys and girls similarly before puberty, but girls are more likely to suffer from migraine afterwards. [4] [6] [10]

AETIOLOGY/ RISK FACTORS

The cause of migraine headaches is unknown. We found few reliable data identifying risk factors or measuring their effects in children. Suggested risk factors include stress, foods, menses, and exercise in genetically predisposed children. [10] [11]

PROGNOSIS

We found no reliable data about the prognosis of childhood migraine headache diagnosed by IHS criteria. Psychological factors that contribute to symptoms should be taken into account when considering expectations for treatment success. Not all treatments work for every child: some will be non-responders to medicines with the clearest evidence available from controlled trials to support their use. It has been suggested that more than half of children will have spontaneous remission after puberty. [10] Migraine that develops during adolescence often continues in adult life, although attacks tend to be less frequent and severe over time. [12] We found one longitudinal study from Sweden (73 children with "pronounced" migraine and mean age onset of 6 years) with >40 years' follow-up, which predated the IHS criteria for migraine headache. [13] It found that migraine headaches had ceased before the age of 25 years in 23% of people. However, by the age of 50 years, more than half of people continued to have migraine headaches. We found no prospective data examining long-term risks in children with migraine.

AIMS OF INTERVENTION

To provide relief from symptoms; to prevent recurrent attacks in the long term; to minimise the disruption of childhood activities, with minimal adverse effects.

OUTCOMES

Symptom relief: pain, often measured on visual analogue scales; nausea; duration and frequency of headache; **functional impairment:** measured by behavioural scores, sleep scores, sleep satisfaction scores; **migraine recurrence**; **adverse effects of treatment**. Migraine index is a validated scale for measuring severity in adult migraine. Its validity in children is unclear.

METHODS

Clinical Evidence search and appraisal June 2010. The following databases were used to identify studies for this systematic review: Medline 1966 to June 2010, Embase 1980 to June 2010, and The Cochrane Database of Systematic Reviews, Issue 2, 2010 (1966 to date of issue). An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language and containing >20 individuals of whom >80% were followed up. There was no minimum length of follow-up required to include studies apart from the prophylaxis studies, where only those of at least 1 month follow-up were included. We excluded RCTs where participants did not fulfil IHS criteria for migraine. We included all studies described as "blinded", "open", "open label", or not blinded as there are so few data available. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. In addition we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 30). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of treatments for acute attacks of migraine headache in children?

OPTION PARACETAMOL

- For GRADE evaluation of interventions for Migraine headache in children, see table, p 30 .
- We don't know whether paracetamol relieves the pain of migraine in children, as we found few trials. Nevertheless, it is widely accepted good clinical practice that paracetamol should be offered unless contraindicated.
- **Note:**
  The FDA issued a drug safety alert on the risk of rare but serious skin reactions with paracetamol (acetaminophen) (August 2013).

Benefits and harms

Paracetamol versus placebo:

We found 5 systematic reviews (search dates not reported, [14] 2004, [15] [16] 2003, [17] 2007 [18]). All reviews identified the same single RCT [19] that did not meet *Clinical Evidence* inclusion criteria (see further information on studies). For further information about symptoms and treatment of paracetamol overdose, see our review on paracetamol poisoning.

Further information on studies

[19] The three-way crossover RCT (106 children) comparing paracetamol, ibuprofen, and placebo had high withdrawal rates (17%) and did not report results before crossover. This may have introduced bias because of continued treatment effects after crossover, and because of unequal withdrawals among groups.

Comment:

Clinical guide:
Despite the absence of strong evidence from RCTs, it is widely accepted good clinical practice that children who have migraine should be offered paracetamol unless contraindicated. [20]

OPTION NSAIDS

- For GRADE evaluation of interventions for Migraine headache in children, see table, p 30 .
- We don't know whether NSAIDs relieve the pain of migraine in children, as we found few trials. Nevertheless, it is widely accepted good clinical practice that children who have migraine should be offered NSAIDs such as ibuprofen unless contraindicated.

Benefits and harms

Ibuprofen versus placebo:

We found two systematic reviews (search dates not reported, [14] 2007 [18]), which identified the same two RCTs. The second review did not pool data, so we do not report it further. [18] However, the second review [18] included one further RCT [21] published subsequent to the first review, which we report separately from the original report.

Symptom relief

Compared with placebo Ibuprofen may be more effective for pain relief (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[14] Systematic review	242 children aged <17 years 2 RCTs in this analysis	**Proportion of children with headache relief , 2 hours** 73/125 (58%) with ibuprofen (7.5–10 mg/kg) 45/117 (38%) with placebo Headache response was defined as an improvement of 2 units in visual analogue pain scales	RR 1.50 95% CI 1.15 to 1.96 Both RCTs included in the meta-analysis had methodological flaws that compromised the validity of their results, including failure to report results before crossover and high withdrawal rates	●○○	ibuprofen
[14] Systematic review	242 children aged <17 years 2 RCTs in this analysis	**Proportion of children who were pain free , 2 hours** 52/125 (42%) with ibuprofen (7.5–10 mg/kg) 25/117 (21%) with placebo	RR 1.92 95% CI 1.28 to 2.86 Both RCTs included in the meta-analysis had methodological flaws that compromised the validity of their results, including failure to report results before crossover and high withdrawal rates	●○○	ibuprofen
[21] RCT **3-armed trial**	32 children, 29 (90%) of whom were included in the intention-to-treat analysis In review [18] Data from 1 RCT The remaining arm evaluated zolmitriptan	**Proportion of children with pain relief , 1 hour** 45% with ibuprofen (200–400 mg single dose) 7% with placebo Absolute numbers not reported Pain was measured on a 4-point scale (none, mild, moderate, or severe), and pain relief was defined as no or mild headache after moderate or severe headache	P <0.01 The RCT made statistical adjustments for related samples when comparing ibuprofen versus placebo	○○○	ibuprofen
[21] RCT **3-armed trial**	32 children, 29 (90%) of whom were included in the intention-to-treat analysis In review [18] Data from 1 RCT The remaining arm evaluated zolmitriptan	**Proportion of children with pain relief , 2 hours** 69% with ibuprofen 28% with placebo Absolute numbers not reported Pain was measured on a 4-point scale (none, mild, moderate, or severe), and pain relief was defined as no or mild headache after moderate or severe headache	P <0.05 The RCT made statistical adjustments for related samples when comparing ibuprofen versus placebo	○○○	ibuprofen

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[21] RCT **3-armed trial**	32 children, 29 (90%) of whom were included in the intention-to-treat analysis In review [18] The remaining arm evaluated zolmitriptan	**Proportion of children with pain relief , 4 hours** 86% with ibuprofen 48% with placebo Absolute numbers not reported Pain was measured on a 4-point scale (none, mild, moderate, or severe), and pain relief was defined as no or mild headache after moderate or severe headache	P <0.01 The RCT made statistical adjustments for related samples when comparing ibuprofen versus placebo	○○○	ibuprofen
Nausea					
[21] RCT **3-armed trial**	32 children, 29 (90%) of whom were included in the intention-to-treat analysis In review [18] The remaining arm evaluated zolmitriptan	**Proportion of children with nausea , 1 hour** 41% with ibuprofen 76% with placebo Absolute numbers not reported	P <0.01 The RCT made statistical adjustments for related samples when comparing ibuprofen versus placebo	○○○	ibuprofen
[21] RCT **3-armed trial**	32 children, 29 (90%) of whom were included in the intention-to-treat analysis In review [18] The remaining arm evaluated zolmitriptan	**Proportion of children with nausea , 2 hours** 14% with ibuprofen 62% with placebo Absolute numbers not reported	P <0.01 The RCT made statistical adjustments for related samples when comparing ibuprofen versus placebo	○○○	ibuprofen

Functional impairment

No data from the following reference on this outcome. [14] [21]

Migraine recurrence

No data from the following reference on this outcome. [14] [21]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[21] RCT **3-armed trial**	32 children, 29 (90%) of whom were included in the intention-to-treat analysis In review [18]	**Proportion of children with adverse effects** 28% with ibuprofen 13% with placebo Absolute numbers not reported	P reported as not significant P value not reported	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	The remaining arm evaluated zolmitriptan	Adverse effects were not specified other than to state that they were primarily gastrointestinal or nervous-system related			

No data from the following reference on this outcome. [14]

Other NSAIDs versus placebo:

We found no RCTs.

Further information on studies

Comment: None.

Clinical guide:
Despite the absence of strong evidence from large RCTs, it is widely accepted good clinical practice that children who have migraine should be offered NSAIDs such as ibuprofen unless contraindicated. [20]

OPTION CODEINE PHOSPHATE

- For GRADE evaluation of interventions for Migraine headache in children, see table, p 30 .
- We found no direct information from RCTs about the effects of codeine phosphate in the treatment of children with migraine headache.

Benefits and harms

Codeine versus placebo:

We found no systematic review or RCTs.

Further information on studies

Comment: **Clinical guide:**
Known adverse effects of codeine include nausea, vomiting, constipation, drowsiness, potential for respiratory depression in overdose, difficulty in micturition, and dry mouth.

Although the use of codeine in this clinical setting has not been effectively evaluated, it would seem reasonable to use it for the relief of acute headache refractory to simple analgesics.

OPTION 5HT1 ANTAGONISTS

- For GRADE evaluation of interventions for Migraine headache in children, see table, p 30 .

- There is increasing RCT evidence that nasal sumatriptan is likely to be beneficial in reducing pain at 2 hours compared with placebo in children aged 12 to 17 years with persisting headache.
- We found limited evidence that oral almotriptan may be more effective than placebo at reducing pain at 2 hours, but not at reducing recurrence.
- Oral rizatriptan may reduce nausea but has not been shown to reduce pain compared with placebo.
- We don't know whether oral zolmitriptan or eletriptan are effective compared with placebo; data regarding zolmitriptan are conflicting and data regarding eletriptan are limited.

Benefits and harms

Sumatriptan versus placebo:

We found one systematic review (search date not reported, 5 RCTs, 1475 children aged <17 years) comparing sumatriptan (primarily intranasal) versus placebo. [14]

Symptom relief

Compared with placebo Nasal sumatriptan seems more effective at reducing symptoms of migraine (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[14] Systematic review	963 children aged <17 years 5 RCTs in this analysis	**Proportion of children with headache relief , 2 hours** 308/474 (65%) with nasal sumatriptan (single dose 20–50 mg) 254/493 (51%) with placebo Headache response was defined as an improvement of 2 units in visual analogue pain scales	RR 1.26 95% CI 1.13 to 1.41 Several RCTs included in the meta-analysis had weak methods, which may have confounded results, including: failure to report pre-crossover results, high withdrawal rates, and a protocol allowing use of rescue medications	●○○	sumatriptan
[14] Systematic review	718 children aged <17 years 4 RCTs in this analysis	**Proportion of children who were pain free , 2 hours** 144/356 (40%) with nasal sumatriptan (single dose 20–50 mg) 94/362 (26%) with placebo	RR 1.56 95% CI 1.26 to 1.93 Several RCTs included in the meta-analysis had weak methods, which may have confounded results, including: failure to report pre-crossover results, high withdrawal rates, and a protocol allowing use of rescue medications	●○○	sumatriptan

Functional impairment

No data from the following reference on this outcome. [14]

Migraine recurrence

No data from the following reference on this outcome. [14]

Adverse effects

Compared with placebo Sumatriptan seems to increase taste disturbance (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Taste disturbance					
[22] RCT	653 adolescents (aged 12–17 years), 510 included in the intention-to-treat analysis In review [14]	**Taste disturbance** 60/238 (25%) with sumatriptan 20 mg 4/245 (2%) with placebo 48/255 (19%) with sumatriptan 5 mg	Significance not assessed		
[23] RCT **Crossover design**	129 children, 94 included in the intention-to-treat analysis In review [14]	**Taste disturbance** 26/90 (29%) attacks with sumatriptan 3/87 (3%) attacks with placebo	P <0.001 The results of the RCT should be interpreted with caution as it randomised children but assessed results in relation to number of attacks	○○○	placebo
Adverse effects other than taste disturbance					
[22] RCT	653 adolescents (aged 12 to 17 years), 510 included in the intention-to-treat analysis In review [14]	**Adverse effects (other than taste disturbance)** with sumatriptan 20 mg with placebo with sumatriptan 5 mg The study found no significant difference between groups in rates of other adverse effects		⟷	Not significant
[23] RCT **Crossover design**	129 children, 94 included in the intention-to-treat analysis In review [14]	**Adverse effects (other than taste disturbance)** with sumatriptan with placebo The study found no significant difference between groups in rates of other adverse effects	The results of the RCT should be interpreted with caution as it randomised children but assessed results in relation to number of attacks	⟷	Not significant

No data from the following reference on this outcome. [14]

Rizatriptan versus placebo:

We found one systematic review, [14] which identified one RCT comparing oral rizatriptan versus placebo. [24] We also found one subsequent RCT comparing oral rizatriptan versus placebo that did not meet *Clinical Evidence* inclusion criteria (see further information on studies). [25]

Symptom relief

Compared with placebo Rizatriptan is no more effective at relieving pain at 2 hours, but is more effective at relieving nausea (high-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[24] RCT	360 children aged 12 to 17 years In review [14]	**Complete pain relief , at 2 hours** 48/149 (32%) with rizatriptan 40/142 (28%) with placebo	P = 0.47	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[24] RCT	360 children aged 12 to 17 years In review [14]	**Partial pain relief , at 2 hours** 98/149 (66%) with rizatriptan 80/142 (56%) with placebo	P = 0.08	⟷	Not significant

Functional impairment

No data from the following reference on this outcome. [14]

Migraine recurrence

No data from the following reference on this outcome. [14]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[24] RCT	360 children aged 12 to 17 years In review [14]	**Adverse effects** with rizatriptan with placebo The RCT reported that one child taking rizatriptan developed transient jaundice and hyperglycaemia, which resolved within 1 week	Significance not assessed		

Zolmitriptan versus placebo:

We found one systematic review (search date not reported), [14] which identified one RCT comparing 4 interventions: oral zolmitriptan 10 mg, 5 mg, or 2.5 mg, or placebo. The RCT only performed a direct comparison of zolmitriptan 10 mg versus placebo. [26] We also found two subsequent RCTs. [21] [27] The first subsequent RCT compared zolmitriptan (single dose 2.5 mg) versus placebo versus ibuprofen. [21] The second subsequent RCT did not meet *Clinical Evidence* inclusion criteria (see further information on studies). [27]

Symptom relief

Compared with placebo We don't know whether zolmitriptan is more effective at reducing symptoms of migraine (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[26] RCT **4-armed trial**	850 children aged 12 to 17 years, 699 (82%) treated for at least one migraine attack In review [14]	**Proportion who responded , 2 hours** 54% with zolmitriptan (10 mg) 58% with placebo	Reported as not significant	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	The remaining arms evaluated zolmitriptan 5 mg and zolmitriptan 2.5 mg	Pain intensity was recorded on a 4-point scale, where 0 = no pain and 4 = severe pain Response was defined as improvement in headache pain intensity to mild or no pain. The higher response rates to placebo makes the trial results difficult to interpret			
[26] RCT **4-armed trial**	850 children aged 12 to 17 years, 699 (82%) treated for at least one migraine attack In review [14] The remaining arms evaluated zolmitriptan 5 mg and zolmitriptan 2.5 mg	**Proportion of children who were pain free , 2 hours** 25% with zolmitriptan (10 mg) 20% with placebo Pain intensity was recorded on a 4-point scale, where 0 = no pain and 4 = severe pain	Reported as not significant	⟷	Not significant
[21] RCT **3-armed trial**	32 children, 29 (90%) of whom were included in the intention-to-treat analysis The remaining arm evaluated ibuprofen	**Proportion of children with pain relief , 1 hour** 45% with zolmitriptan 7% with placebo Absolute numbers not reported Pain was measured on a 4-point scale (none, mild, moderate, or severe) and pain relief was defined as no or mild headache after moderate or severe headache	P <0.01 The RCT made statistical adjustments for related samples when comparing zolmitriptan versus placebo	○○○	zolmitriptan
[21] RCT **3-armed trial**	32 children, 29 (90%) of whom were included in the intention-to-treat analysis The remaining arm evaluated ibuprofen	**Proportion of children with pain relief , 2 hours** 62% with zolmitriptan 28% with placebo Absolute numbers not reported Pain was measured on a 4-point scale (none, mild, moderate, or severe) and pain relief was defined as no or mild headache after moderate or severe headache	P <0.05 The RCT made statistical adjustments for related samples when comparing zolmitriptan versus placebo	○○○	zolmitriptan
[21] RCT **3-armed trial**	32 children, 29 (90%) of whom were included in the intention-to-treat analysis The remaining arm evaluated ibuprofen	**Proportion of children with pain relief , 4 hours** 83% with zolmitriptan 4% with placebo Absolute numbers not reported Pain was measured on a 4-point scale (none, mild, moderate, or severe) and pain relief was defined as no or mild headache after moderate or severe headache	P <0.01 The RCT made statistical adjustments for related samples when comparing zolmitriptan versus placebo	○○○	zolmitriptan

Functional impairment

No data from the following reference on this outcome. [21] [26]

Migraine recurrence

No data from the following reference on this outcome. [21] [26]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[26] RCT **4-armed trial**	850 children aged 12 to 17 years, 699 (82%) treated for at least one migraine attack In review [14]	**Proportion of children with adverse effects** 79/178 (44%) with zolmitriptan 10 mg 45/174 (26%) with zolmitriptan 5 mg 49/171 (29%) with zolmitriptan 2.5 mg 22/176 (13%) with placebo Details of adverse effects were not reported	Significance not assessed		
[21] RCT **3-armed trial**	32 children, 29 (90%) of whom were included in the intention-to-treat analysis 3 RCTs in this analysis The remaining arm evaluated ibuprofen	**Proportion of children with adverse effects** 34% with zolmitriptan 13% with placebo Absolute numbers not reported Details of adverse effects were not reported	P <0.05	○○○	placebo

Eletriptan versus placebo:

We found one RCT comparing eletriptan 40 mg versus placebo. [28]

Symptom relief

Compared with placebo We don't know whether eletriptan is more effective at reducing symptoms of migraine (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[28] RCT	348 children aged 12 to 17 years with moderate or severe headache pain (the intention-to-treat population consisted of 274 [80%] participants who completed treatment consistent with the study protocol)	**Proportion of children with headache response , 2 hours** 80/141 (56.7%) with eletriptan 76/133 (57.1%) with placebo Headache response was defined as improvement in headache pain intensity from moderate to severe at baseline to mild or no pain after treatment	P >0.05	⟷	Not significant

Functional impairment

No data from the following reference on this outcome. [28]

Migraine recurrence

No data from the following reference on this outcome. [28]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[28] RCT	348 children aged 12 to 17 years with moderate or severe headache pain (the intention-to-treat population consisted of 274 [80%] participants who completed treatment consistent with the study protocol)	**Adverse effects** 43% with eletriptan 28% with placebo Absolute numbers not reported Adverse effects, including somnolence and dizziness	Significance not assessed P value not reported		

Almotriptan versus placebo:

We found one RCT (866 participants aged 12–17 years) in which people were randomised to treat one migraine headache with either almotriptan (3 different doses tested) or placebo. [29] The RCT did not reach specified end points to separately analyse different doses of almotriptan, so reported analyses should be considered exploratory (see further information on studies, below). [29]

Symptom relief

Compared with placebo Oral almotriptan may be more effective than placebo at improving pain relief at 2 hours in participants aged 12 to 17 years; however, evidence was limited (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[29] RCT **4-armed trial**	866 participants aged 12 to 17 years with a >1-year history of migraine; final analysis consisted of 714 (82%) participants who completed the study protocol The remaining arms assessed oral almotriptan 12.5 mg and 25 mg	**Proportion of participants with headache relief , 2 hours** 72% with almotriptan 6.25 mg 55% with placebo Absolute results reported graphically Pain relief defined as reduction in pain intensity from moderate to severe at baseline to mild or no pain 347 participants in this analysis See further information on studies for subgroup analysis by age	P = 0.001 Result not adjusted for baseline severity Results should be interpreted with caution (see further information on studies)	○○○	almotriptan

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[29] RCT **4-armed trial**	866 participants aged 12 to 17 years with a >1-year history of migraine; final analysis consisted of 714 (82%) participants who completed the study protocol The remaining arms assessed oral almotriptan 6.25 mg and 25 mg	**Proportion of participants with headache relief , 2 hours** 73% with almotriptan 12.5 mg 55% with placebo Absolute results reported graphically Headache relief defined as reduction in pain intensity from moderate to severe at baseline to mild or no pain 351 participants in this analysis See further information on studies for subgroup analysis by age	P <0.001 Result not adjusted for baseline severity Results should be interpreted with caution (see further information on studies)	○○○	almotriptan
[29] RCT **4-armed trial**	866 participants aged 12 to 17 years with a >1-year history of migraine; final analysis consisted of 714 (82%) participants who completed the study protocol The remaining arms assessed oral almotriptan 6.25 mg and 12.5 mg	**Proportion of participants with headache relief , 2 hours** 67% with almotriptan 25 mg 55% with placebo Absolute results reported graphically Headache relief defined as reduction in pain intensity from moderate to severe at baseline to mild or no pain 356 participants in this analysis See further information on studies for subgroup analysis by age	P = 0.028 Result not adjusted for baseline severity Results should be interpreted with caution (see further information on studies)	○○○	almotriptan
[29] RCT **4-armed trial**	866 participants aged 12 to 17 years with a >1-year history of migraine; final analysis consisted of 714 (82%) participants who completed the study protocol Subgroup analysis The remaining arms assessed oral almotriptan 12.5 mg and 25 mg	**Proportion of participants with sustained headache relief , 2 to 24 hours** 67% with almotriptan 6.25 mg 54% with placebo Absolute results reported graphically Sustained headache relief defined as relief at 2 hours, no recurrence, and no rescue medication 2 to 24 hours after dosing Subgroup analysis in participants with headache relief at 2 hours See further information on studies for subgroup analysis by age	P = 0.005 Result not adjusted for baseline severity Results should be interpreted with caution (see further information on studies)	○○○	almotriptan
[29] RCT **4-armed trial**	866 participants aged 12 to 17 years with a >1-year history of migraine; final analysis consisted of 714 (82%) participants who completed the study protocol Subgroup analysis The remaining arms assessed oral almotriptan 6.25 mg and 25 mg	**Proportion of participants with sustained headache relief , 2 to 24 hours** 67% with almotriptan 12.5 mg 54% with placebo Absolute results reported graphically Sustained headache relief defined as relief at 2 hours, no recurrence, and no rescue medication 2 to 24 hours after dosing Subgroup analysis in participants with headache relief at 2 hours See further information on studies for subgroup analysis by age	P = 0.006 Result not adjusted for baseline severity Results should be interpreted with caution (see further information on studies)	○○○	almotriptan

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[29] RCT **4-armed trial**	866 participants aged 12 to 17 years with a >1-year history of migraine; final analysis consisted of 714 (82%) participants who completed the study protocol The remaining arms assessed oral almotriptan 6.25 mg and 12.5 mg	**Proportion of participants with sustained headache relief , 2 to 24 hours** 64% with almotriptan 25 mg 54% with placebo Absolute results reported graphically Sustained headache relief defined as relief at 2 hours, no recurrence, and no rescue medication 2 to 24 hours after dosing Subgroup analysis in participants with headache relief at 2 hours See further information on studies for subgroup analysis by age	P = 0.02 Result not adjusted for baseline severity Results should be interpreted with caution (see further information on studies)	○○○	almotriptan

Migraine recurrence

Compared with placebo We don't know whether oral almotriptan is more effective at reducing the proportion of people with migraine recurrence or the need for rescue medication at 2 to 24 hours in people aged 12 to 17 years (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Migraine recurrence					
[29] RCT **4-armed trial**	866 participants aged 12 to 17 years with a >1-year history of migraine; final analysis consisted of 714 (82%) participants who completed the study protocol Subgroup analysis	**Proportion of participants with migraine recurrence , between 2 and 24 hours** 6% with almotriptan 6.25 mg 8% with almotriptan 12.5 mg 3% with almotriptan 25 mg 5% with placebo Absolute numbers not reported Subgroup analysis of participants with headache relief at 2 hours	P value not reported Reported as not significant for any dose of almotriptan *v* placebo	⟷	Not significant
[29] RCT **4-armed trial**	866 participants aged 12 to 17 years with a >1-year history of migraine; final analysis consisted of 714 (82%) participants who completed the study protocol	**Proportion of participants using rescue medication , between 2 and 24 hours** 2.8% with almotriptan 6.25 mg 5.0% with almotriptan 12.5 mg 3.2% with almotriptan 25 mg 6.5% with placebo Absolute numbers not reported Subgroup analysis of participants with headache relief at 2 hours	P values not reported Reported as not significant for any dose of almotriptan *v* placebo	⟷	Not significant

Functional impairment

No data from the following reference on this outcome. [29]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[29] RCT **4-armed trial**	866 participants aged 12 to 17 years with a >1-year history of migraine; final analysis consisted of 714 (82%) participants who completed the study protocol	**Proportion of people with at least one adverse effect** 27/177 (15%) with almotriptan 6.25 mg 43/181 (24%) with almotriptan 12.5 mg 48/186 (26%) with almotriptan 25 mg 32/170 (19%) with placebo The most common adverse effects reported were dizziness, somnolence, and nausea See further information on studies for subgroup analysis by age	P values not reported Reported as not significant for any dose of almotriptan versus placebo		

Further information on studies

[25] The RCT (147 children aged 6–16 years, crossover design) comparing oral rizatriptan versus placebo did not meet *Clinical Evidence* inclusion criteria, as only 96/147 (65%) children completed the trial

[27] The RCT had a crossover design and did not meet *Clinical Evidence* inclusion criteria, as it did not report results pre-crossover.

[28] Post-hoc analysis found that eletriptan was significantly more effective than placebo in achieving a sustained headache response at 24 hours after treatment (proportion with sustained response: 73/141 [52%] with eletriptan *v* 52/133 [39%] with placebo; P <0.05).

[29] The RCT reported that a prespecified criterion for analysing all dosage groups was that almotriptan 25 mg had to be shown to be significantly better than placebo for all 4 primary end points (headache relief at 2 hours, nausea, photophobia, phonophobia). The 2-hour pain-relief rate adjusted for baseline severity was significantly better with almotriptan 25 mg compared with placebo (67% with almotriptan *v* 55% with placebo; P = 0.022). However, there were no significant differences between groups at 2 hours for nausea, photophobia, and phonophobia. The RCT reported that, in accordance with the protocol, stepwise comparisons of almotriptan 12.5 mg and 6.25 mg were not performed, and that all the subsequent analyses reported should be considered exploratory.

[29] The RCT randomised children in a 1:1:1:1 ratio in two age groups (12–14 years and 15–17 years), although it did not provide the absolute numbers of children in either age group. Subgroup analysis found significantly greater 2-hour headache relief for the three different doses of almotriptan in children aged 15 to 17 years compared with placebo, but no significant difference between all doses of almotriptan and placebo in the younger age group (12–14 years). The RCT reported subgroup analyses by age for nausea and photophobia 2 hours post dose, although it did not report the overall results. The RCT reported no significant differences between any dose of almotriptan and placebo in the proportion of participants with nausea (participants aged 15–17 years; nausea: 14.8% with almotriptan 6.25 mg *v* 18.8% with 12.5 mg *v* 18.4% with 25 mg *v* 15.2% with placebo; participants aged 12–14 years: 13% with almotriptan 6.25 mg *v* 15% with 12.5 mg *v* 23% with 25 mg *v* 16% with placebo; P values not reported; reported as not significant). Only almotriptan 12.5 mg significantly decreased photophobia compared with placebo (participants aged 15–17 years; photophobia: 39% with almotriptan 6.25 mg *v* 28% with 12.5 mg *v* 36% with 25 mg *v* 44% with placebo; participants aged 12–14 years: 28% with almotriptan 6.25 mg *v* 22% with 12.5 mg *v* 34% with 25 mg *v* 37% with placebo; P <0.05 for almotriptan 12.5 mg *v* placebo in both age groups; P values not reported for other doses *v* placebo; reported as not significant). **Adverse effects** Adverse-effect profiles were similar for both age groups.

Comment: **Clinical guide:**
There is some evidence to support the use of nasal sumatriptan and oral almotriptan for the relief of acute symptoms in children.

OPTION ANTIEMETICS

- For GRADE evaluation of interventions for Migraine headache in children, see table, p 30 .
- We don't know whether antiemetics are beneficial for treating acute attack of childhood migraine, as we found no RCTs.

Benefits and harms

Antiemetics:

We found no systematic review or RCTs.

Further information on studies

Comment: The use of antiemetics in treating migraine in children has not been effectively evaluated.

QUESTION What are the effects of prophylaxis for migraine headache in children?

OPTION BETA-BLOCKERS

- For GRADE evaluation of interventions for Migraine headache in children, see table, p 30 .
- Studies of beta-blockers as prophylaxis in children have given inconsistent results, and propranolol may even increase the duration of headaches compared with placebo.

Benefits and harms

Propranolol versus placebo:

We found three systematic reviews (search dates 2007, [30] 2004, [31] 2002 [32]). None of the reviews performed a meta-analysis owing to heterogeneity of outcome data reported, so we report the results of the individual RCTs that met *Clinical Evidence* quality criteria here. The reviews all identified the same three RCTs. [33] [34] [35]

Symptom relief

Compared with placebo We don't know whether propranolol is more effective at preventing symptoms of migraine headache in children (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom relief					
[33] RCT **Crossover design**	32 children aged 7 to 16 years (13% of people were lost to follow-up) In review [30] [31] [32]	**Proportion reporting "some benefit" , during a 3-month period** 13/13 (100%) with propranolol (60–120 mg/day divided in 3 doses) 4/15 (27%) with placebo Pre-crossover results	P <0.001 Reliability of result may be limited because of loss to follow-up and the clinical relevance of the reported outcome is unclear	○○○	propranolol
[34] RCT **Crossover design**	53 children aged 9 to 15 years In review [30] [31] [32]	**Mean duration of headache** 436 minutes with propranolol (40–120 mg daily) 287 minutes with placebo Pre-crossover results	P <0.01	○○○	placebo

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[35] RCT **Crossover design**	33 children aged 6 to 12 years In review [30] [31] [32] In 5 children (15%) in whom migraine was thought to be provoked by food, diet was restricted to avoid certain foods (no details about type of foods reported)	**Mean number of headaches , at 3 months** 14.9 with propranolol (3 mg/kg daily) 13.3 with placebo Pre-crossover results	P = 0.47 Dietary restriction may have confounded apparent treatment effects	⟷	Not significant

Functional impairment

No data from the following reference on this outcome. [33] [34] [35]

Migraine recurrence

No data from the following reference on this outcome. [33] [34] [35]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[33] RCT **Crossover design**	32 children aged 7 to 16 years In review [30] [31] [32]	**Adverse effects** with propranolol with placebo 2/13 (15%) of children taking propranolol had insomnia, but the RCT did not report on adverse effects in the placebo group	Significance not assessed		
[34] RCT **Crossover design**	53 children aged 9 to 15 years In review [30] [31] [32]	**Number of children with adverse effects** 12 with propranolol 12 with placebo Adverse effects in both groups included abdominal pain, increased appetite, worsening of headaches, and fatigue	Reported as not significant However, the trial was too small to yield reliable information about harms	⟷	Not significant

No data from the following reference on this outcome. [35]

Timolol versus placebo:

We found three systematic reviews (search dates 2007, [30] 2004, [31] 2002 [32]), which identified one RCT that did not meet *Clinical Evidence* inclusion criteria (see further information on studies). [36]

Other beta-blockers versus placebo:

We found three systematic reviews (search dates 2007, [30] 2004, [31] 2002 [32]), which identified no RCTs.

Further information on studies

[36] The RCT (19 children) was too small and methodologically flawed to meet *Clinical Evidence* inclusion criteria.

Comment: For the use of beta-blockade in this setting, the results of RCTs are inconclusive. Further evaluation in larger trials should be undertaken if feasible.

OPTION PIZOTIFEN

- For GRADE evaluation of interventions for Migraine headache in children, see table, p 30 .
- Pizotifen is widely used as prophylaxis in children with migraine, but we found no RCTs assessing its efficacy.

Benefits and harms

Pizotifen versus placebo:

We found 4 systematic reviews (search dates 2007, [30] 2004, [31] [16] 2002 [32]), all of which identified the same two RCTs, [37] [38] neither of which met *Clinical Evidence* inclusion criteria (see further information on studies).

Further information on studies

[37] The RCT (47 children aged 7–14 years) pre-dated the International Headache Society (IHS) diagnostic criteria for migraine and children included did not fulfil the current IHS definition criteria.

[38] The RCT has only been published in abstract form and so we could not reliably review its methods.

Comment: **Clinical guide:**
Although pizotifen is almost universally used for paediatric migraine, there is no evidence from well-conducted trials that it is beneficial. RCTs would be feasible and should be undertaken.

OPTION TOPIRAMATE

- For GRADE evaluation of interventions for Migraine headache in children, see table, p 30 .
- There is some inconclusive RCT evidence that topiramate may be useful as prophylaxis in children with migraine.

Benefits and harms

Topiramate versus placebo:

We found three systematic reviews (search dates 2007 [39] [30] 2008 [40]). The first two reviews identified the same RCT. [41] The third systematic review, [40] which did not perform a meta-analysis, identified two RCTs, [41] [42] including the one identified by the two earlier reviews, [41] and so we report only the most recent review here. [40] We also found one subsequent RCT [43] and one further report of the subsequent RCT that evaluated adverse effects. [44]

Symptom relief

Compared with placebo Topiramate may be more effective at reducing headache frequency over 3 to 5 months. However, results varied between RCTs and by the outcome measure analysed (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Migraine frequency					
[41] RCT	162 children aged 6 to 15 years In review [40]	**Mean reduction in monthly migraine days , over 5 months** 2.6 days with topiramate 2.0 days with placebo	P = 0.06	⟷	Not significant
[41] RCT	162 children aged 6 to 15 years In review [40]	**Mean reduction in monthly migraine days , last 28 days of treatment** 3.1 days with topiramate 2.4 days with placebo	P = 0.02	○○○	topiramate
[41] RCT	162 children aged 6 to 15 years In review [40]	**Proportion of children with >50% reduction in monthly migraine days , 5 months** 55% with topiramate 47% with placebo Absolute results reported graphically	P = 0.39	⟷	Not significant
[41] RCT	162 children aged 6 to 15 years In review [40]	**Proportion of children with >75% reduction in monthly migraine days , 5 months** 32% with topiramate 14% with placebo Absolute results reported graphically	P = 0.02	○○○	topiramate
[41] RCT	162 children aged 6 to 15 years In review [40]	**Proportion of children with >50% reduction in mean monthly days of migraine , last 28 days of treatment** 70% with topiramate 53% with placebo Absolute results reported graphically	P = 0.05	⟷	Not significant
[41] RCT	162 children aged 6 to 15 years In review [40]	**Proportion of children with >75% reduction in mean monthly days of migraine , last 28 days of treatment** 51% with topiramate 31% with placebo Absolute results reported graphically	P = 0.02	○○○	topiramate
[41] RCT	162 children aged 6 to 15 years In review [40]	**Proportion of children who were completely headache free , last 28 days of treatment** 34% with topiramate 20% with placebo Absolute results reported graphically	P = 0.09	⟷	Not significant
[42] RCT	44 children with migraine In review [40]	**Decrease in mean monthly migraine days , 4 months** 11.9 days with topiramate	P = 0.02	○○○	topiramate

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		5.9 days with placebo			
[42] RCT	44 children with migraine In review [40]	**Proportion of children with >50% reduction in monthly migraine days , 4 months** 20/21 (95%) with topiramate 11/21 (52%) with placebo Absolute results reported graphically	P = 0.002	○○○	topiramate
[43] RCT **3-armed trial**	106 participants aged 12 to 17 years with at least a 6-month history of migraine The remaining arm assessed topiramate 100 mg daily	**Mean % reduction in monthly migraine attack , last 12 weeks of a 16-week treatment period** 34% with topiramate 50 mg daily 42% with placebo 68 participants in this analysis	P = 0.80	⟷	Not significant
[43] RCT **3-armed trial**	106 participants aged 12 to 17 years with at least a 6-month history of migraine The remaining arm assessed topiramate 50 mg daily	**Mean % reduction in monthly migraine attack , last 12 weeks of a 16-week treatment period** 70% with topiramate 100 mg daily 42% with placebo 68 participants in this analysis Children were randomised to treatment in a ratio of 1:1:1 after being stratified by age into 2 groups (12–14 years; 15–17 years)	P = 0.02	○○○	topiramate
[43] RCT **3-armed trial**	106 participants aged 12 to 17 years with at least a 6-month history of migraine The remaining arm assessed topiramate 100 mg daily	**Mean % reduction in monthly migraine day rate , last 12 weeks of a 16-week treatment period** 35% with topiramate 50 mg daily 36% with placebo 68 participants in this analysis	P = 0.70	⟷	Not significant
[43] RCT **3-armed trial**	106 participants aged 12 to 17 years with at least a 6-month history of migraine The remaining arm assessed topiramate 50 mg daily	**Mean % reduction in monthly migraine day rate , last 12 weeks of a 16-week treatment period** 71% with topiramate 100 mg daily 36% with placebo 68 participants in this analysis	P = 0.002	○○○	topiramate

Functional impairment

No data from the following reference on this outcome. [41] [42] [43]

Migraine recurrence

No data from the following reference on this outcome. [41] [42] [43]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[41] RCT	162 children aged 6 to 15 years In review [40]	**Adverse effects** with topiramate with placebo There were fewer adverse effects with topiramate, and no serious adverse effects were reported in either group	Significance not assessed		
[42] RCT	44 children with migraine In review [40]	**Proportion of participants who lost weight** 17/21 (81%) with topiramate 3/21 (14%) with placebo	Significance not assessed		
[42] RCT	44 participants with migraine In review [40]	**Proportion of participants with lack of concentration in school** 4/21 (19%) with topiramate 0/21 (0%) with placebo	Significance not assessed		
[42] RCT	44 participants with migraine In review [40]	**Proportion with paraesthesias** 5/21 (24%) with topiramate 0/21 (0%) with placebo	Significance not assessed		
[43] RCT **3-armed trial**	106 participants aged 12 to 17 years with at least a 6-month history of migraine	**Proportion of participants who lost weight (<10% from base-line) , during 16-week treatment period** 28% with topiramate 50 mg daily 48% with topiramate 100 mg daily 22% with placebo Absolute numbers not reported	Significance not assessed		
[43] RCT **3-armed trial**	106 participants aged 12 to 17 years with at least a 6-month history of migraine	**Anorexia , during 16-week treatment period** 3/35 (9%) with topiramate 50 mg daily 4/35 (11%) with topiramate 100 mg daily 1/33 (3%) with placebo	Significance not assessed		
[43] RCT **3-armed trial**	106 participants aged 12 to 17 years with at least a 6-month history of migraine	**Insomnia , during 16-week treatment period** 3/35 (8.6%) with topiramate 50 mg daily 1/35 (2.9%) with topiramate 100 mg daily 1/33 (3.0%) with placebo	Significance not assessed		
[43] RCT **3-armed trial**	106 participants aged 12 to 17 years with at least a 6-month history of migraine	**Fatigue , during 16-week treatment period** 2/35 (5.7%) with topiramate 50 mg daily 3/35 (8.6%) with topiramate 100 mg daily 2/33 (6.1%) with placebo	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[43] RCT **3-armed trial**	106 participants aged 12 to 17 years with at least a 6-month history of migraine	**Dizziness , during 16-week treatment period** 2/35 (6%) with topiramate 50 mg daily 3/35 (9%) with topiramate 100 mg daily 0 (0%) with placebo	Significance not assessed		
[44] RCT **3-armed trial**	106 participants aged 12 to 17 years with at least a 6-month history of migraine Further report of reference [43] The remaining arm assessed topiramate 50 mg daily	**Mean change in reaction time (in milliseconds) , end of a 16-week treatment period** +33.7 with topiramate 100 mg daily –3.5 with placebo 68 participants in this analysis See further information on studies for details of tests used	P = 0.028	○○○	placebo
[44] RCT **3-armed trial**	106 participants aged 12 to 17 years with at least a 6-month history of migraine Further report of reference [43] The remaining arm assessed topiramate 50 mg daily	**Pattern recognition memory: change in mean correct latency (in milliseconds) , end of a 16-week treatment period** +51.3 with topiramate 100 mg daily –132.7 with placebo 68 participants in this analysis See further information on studies for details of tests used	P = 0.027	○○○	placebo
[44] RCT **3-armed trial**	106 participants aged 12 to 17 years with at least a 6-month history of migraine Further report of reference [43] The remaining arm assessed topiramate 50 mg daily	**Change in rapid visual information processing mean latency (in milliseconds) , end of a 16-week treatment period** +23.0 with topiramate 100 mg daily –87.9 with placebo 68 participants in this analysis See further information on studies for details of tests used	P = 0.04	○○○	placebo

Further information on studies

[43] **Adverse effects** The RCT reported that assessment of events of special concern for topiramate (including rash; ocular, renal, and hepatic events; oligohydrosis/hyperthermia; hyperammonaemia/encephalopathy; metabolic acidosis; weight loss; depression/suicide, and suicide-related events) did not reveal any unexpected findings; events were either absent, not clinically relevant, considered by the investigators to be unrelated to topiramate treatment, or consistent with the known safety profile of topiramate.

[44] The trial reported that the Cambridge Neuropsychological Test Automated Battery (CANTAB) and cognitive adverse effects were used to evaluate neurocognitive effects of topiramate. The RCT did not report data for topiramate 50 mg daily versus placebo for the adverse effects reported above, but it reported that the differences between groups were not significant.

Comment: The reviews identified several other RCTs suggesting topiramate as beneficial for migraine prophylaxis in population groups that included children. However, the mean age of participants in each

RCT was at least 33 years, and none of the studies indicated how many participants were children or reported subgroup analyses in children.

OPTION DIETARY MANIPULATION

- For GRADE evaluation of interventions for Migraine headache in children, see table, p 30 .
- We don't know whether prophylactic dietary manipulation can prevent recurrence of migraine in children.

Benefits and harms

Dietary manipulation:

We found one systematic review (search date 2004), [45] which identified 4 RCTs, [46] [47] [48] [49] none of which met *Clinical Evidence* inclusion criteria (see further information on studies).

Further information on studies

[46] The RCT (40 people) had only a 3-week follow-up.

[47] The RCT (27 people) on fish oil used olive oil as a placebo, which is not an inert comparator.

[48] The RCT (61 children) pre-dated the International Headache Society criteria for migraine, and a large proportion (36%) of participants withdrew from treatment.

[49] The RCT assessed oligoantigenic diet (involving exclusion of dietary vasoactive amines). Of the 43 participants, 11 (26%) withdrew from the trial. All participants from the group were randomised to diet.

Comment: **Clinical guide:**
There is little satisfactory evidence of benefit from dietary manipulation, so clinicians may need to rely on observational evidence, plausible biomedical hypotheses, and their own experience to endorse the use of this intervention.

OPTION THERMAL BIOFEEDBACK

- For GRADE evaluation of interventions for Migraine headache in children, see table, p 30 .
- We don't know whether prophylactic thermal biofeedback can prevent recurrence of migraine in children.

Benefits and harms

Thermal biofeedback:

We found two systematic reviews (search dates 2004), [45] [16] which identified no RCTs that met *Clinical Evidence* inclusion criteria.

Further information on studies

Comment: Both reviews identified the same RCT, [50] which used a repeated-measures design to assess outcomes over 6 months, and had a 46% loss to follow-up by 6 months; the design did not allow for independent assessment of results at earlier time frames.

OPTION PROGRESSIVE MUSCLE RELAXATION

- For GRADE evaluation of interventions for Migraine headache in children, see table, p 30 .

- We don't know whether prophylactic progressive muscle relaxation can prevent recurrence of migraine in children.

Benefits and harms

Progressive muscle relaxation versus placebo:

We found two systematic reviews (search dates 2004), [45] [16] which identified one RCT comparing three interventions: progressive muscle relaxation, cognitive coping, and placebo. [51]

Symptom relief

Compared with placebo We don't know whether progressive muscle relaxation reduces headache pain and frequency (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom relief					
[51]	51 children (42/51 [82%] children completed the trial) In review [45] [16]	**Headache index and headache frequency** with progressive muscle relaxation with placebo Absolute results not reported The placebo intervention involved "stress reduction training", so it is unclear whether it was an inert comparator Details of possible total score on the headache index and timescales for measuring headache frequency not reported	P <0.05	○○○	progressive muscle relaxation
[51]	51 children (42/51 [82%] children completed the trial) In review [45] [16]	**Duration of headache or headache peak intensity** with progressive muscle relaxation with placebo Absolute results not reported The placebo intervention involved "stress reduction training", so it is unclear whether it was an inert comparator Details of possible total score on the headache index and timescales for measuring headache frequency were not reported	Reported as not significant	⟷	Not significant

Functional impairment

No data from the following reference on this outcome. [51]

Migraine recurrence

No data from the following reference on this outcome. [51]

Further information on studies

Comment: Both reviews also identified two RCTs that did not meet *Clinical Evidence* inclusion criteria. [52] [53] The first RCT (99 people aged 9–17 years) compared progressive muscle relaxation versus placebo. The placebo was psychological counselling, which is not an inert comparator, and high loss to follow-up (30%) precluded reliable conclusions. [52] The second RCT, which compared three interventions (relaxation alone, thermal biofeedback plus relaxation, and waiting list control) had a 35% loss to follow-up. [53]

Clinical guide:
RCTs with acceptable follow-up rates into the effects of progressive muscle relaxation have not been, and are unlikely to be, undertaken. In recommending this intervention, clinicians may need to rely on observational evidence, plausible biomedical hypotheses, and their own experience.

OPTION STRESS MANAGEMENT

- For GRADE evaluation of interventions for Migraine headache in children, see table, p 30 .
- When used prophylactically, stress management programmes may improve headache severity and frequency in the short term compared with no stress management.

Benefits and harms

Stress management versus no stress management:

We found one systematic review (search date 2004), [45] which identified one RCT. [54] The RCT compared a self-administered stress management programme versus a stress management programme delivered by the clinic versus no stress management.

Symptom relief

Compared with no stress management programme A self-administered stress management programme seems more effective at reducing the frequency and severity of migraine headaches at 1 month (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom relief					
[54] RCT **3-armed trial**	87 people, aged 11 to 18 years In review [45]	**Proportion of children improved in headache severity and frequency , 1 month** 16/24 (67%) with self-administered stress management programme 10/23 (44%) with treatment delivered by the clinic 6/25 (24%) with no stress management	P <0.01 for differences among all 3 groups	○○○	self-administered stress management

Functional impairment

No data from the following reference on this outcome. [54]

Migraine recurrence

No data from the following reference on this outcome. [54]

Adverse effects

No data from the following reference on this outcome. [54]

Further information on studies

Comment: **Clinical guide:**
RCTs with acceptable follow-up rates into the effects of stress management have not and are unlikely to be undertaken. In recommending this intervention, clinicians may need to rely on observational evidence, plausible biomedical hypotheses, and their own experience.

GLOSSARY

Aura A premonitory sensation or warning experienced before the start of a migraine headache.

Crossover trial Administering two interventions one after the other to the same group of patients either randomly or in a specified manner.

Dietary manipulation A change in diet aimed specifically at reducing or removing from the diet a foodstuff that is thought to provoke migraine headache.

Dietary vasoactive amines Dietary amines (protein subunits) that may have an effect on cerebral vascular tone.

Progressive muscle relaxation Volitional muscle relaxation aimed at altering the perception of symptoms such as headache.

Stress management Coping or relaxation strategies that aim to alter the perception of symptoms.

Thermal biofeedback A treatment in which an individual attempts to alter their skin temperature by responding to feedback about their skin temperature.

Cambridge Neuropsychological Test Automated Battery (CANTAB) A battery of computerised neuropsychological tests designed to be non-linguistic, culturally blind, and administered by a trained assistant. Interpretation of a patient's condition is intended to be easily understood by a clinician. Tests include: pattern and spatial recognition memory; spatial span; paired associates learning; reaction time; rapid visual information processing; and controlled oral word association test.

High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.

International Headache Society criteria (1988) *Migraine without aura (common migraine)* is defined as 5 or more headache attacks lasting for 4 to 72 hours with accompanying symptoms of either nausea/vomiting and/or phonophobia and photophobia. Pain should comply with at least two of the following 4 characteristics: unilateral, throbbing, moderate to severe intensity, and increase with physical activity. For *migraine with aura (classic migraine)*, two or more headache attacks are required that comply with three of the following 4 characteristics: one or more fully reversible aura symptom indicating focal cerebral cortical and/or brainstem dysfunction; at least one aura symptom developing gradually over more than 4 minutes or two or more symptoms occurring in succession; no aura symptom should last more than 1 hour; and headache follows aura with a pain free (see below) interval of less than 60 minutes. In both migraine with and without aura, secondary causes of headache should be excluded; if any structural damage is found, then it should not explain headache characteristics. Less stringent criteria for migraine without aura can be used. In clinical practice, the so-called borderline migraine can be diagnosed when one of the above criteria is not met. International Headache Society criteria were not developed with the intention of identifying potential responders to different medications.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

5HT$_1$ antagonists New evidence added. [29] Categorisation unchanged (Beneficial).

NSAIDs New evidence added. [18] Categorisation unchanged (Likely to be beneficial).

Paracetamol New evidence added. [18] Categorisation unchanged (Likely to be beneficial).

Topiramate New evidence added. [40] [43] [44] Categorisation unchanged (Unknown effectiveness) as the RCTs identified gave conflicting results.

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Disclaimer

TABLE 1 **International Headache Society criteria for migraine [1] (text in parentheses indicates suggested revisions for children under 15 years of age). [2]**

	At least 5 episodes without aura fulfilling all of criteria 1–3:	OR	At least 2 episodes with aura fulfilling at least 3 of criteria 1–4:
1.	Headache lasting 2 to 48 hours (30 minutes to 48 hours)	1.	One or more fully reversible aura symptoms including focal cortical, brain stem dysfunction, or both
2.	Headache meeting at least 2 of the following criteria: a) Unilateral or bilateral (either frontal or temporal) distribution of pain b) Throbbing c) Moderate to severe intensity d) Aggravated by routine physical activity	2.	At least 1 aura symptom that develops gradually over >4 minutes, or 2 or more symptoms that occur in succession
3.	At least one of the following symptoms while headache is present: a) Nausea, vomiting, or both b) Photophobia, phonophobia, or both	3.	No aura symptoms lasting >60 minutes
		4.	Headache follows aura within 60 minutes

GRADE **Evaluation of interventions for Migraine headache in children.**

Important outcomes	Adverse effects, Functional impairment, Migraine recurrence, Symptom relief								
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of treatments for acute attacks of migraine headache in children?									
3 (271) [14] [21]	Symptom relief	Ibuprofen versus placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and inclusion of flawed RCTs in meta-analysis
5 (967) [14]	Symptom relief	Sumatriptan versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for poor methodology in some RCTs (failure to report pre-crossover results; high withdrawal rates)
2 (832) [22] [23]	Adverse effects	Sumatriptan versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for weak statistical methods
1 (291) [24]	Symptom relief	Rizatriptan versus placebo	4	0	0	0	0	High	
2 (879) [26] [21]	Symptom relief	Zolmitriptan versus placebo	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results
1 (274) [28]	Symptom relief	Eletriptan versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (866) [29]	Symptom relief	Almotriptan versus placebo	4	–2	0	–1	0	Very low	Quality points deducted for incomplete reporting of results and no intention-to-treat analysis. Directness point deducted for unclear generalisability as results are exploratory (reported although criteria for analysis not achieved)
1 (866) [29]	Migraine recurrence	Almotriptan versus placebo	4	–2	0	–1	0	Very low	Quality points deducted for incomplete reporting of results and no intention-to-treat analysis. Directness point deducted for unclear generalisability as results are exploratory (reported although criteria for analysis not achieved)
What are the effects of prophylaxis for migraine headache in children?									
3 (119) [33] [34] [35]	Symptom relief	Propranolol versus placebo	4	–1	–1	–1	0	Very low	Quality point deducted for sparse data. Consistency point deducted for conflicting results. Directness point deducted for inclusion of co-intervention. We found no direct information about other beta-blockers for prophylaxis of migraine in children
3 (309) [41] [42] [43]	Symptom relief	Topiramate versus placebo	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for wide variation in results across the RCTs

Important outcomes			Adverse effects, Functional impairment, Migraine recurrence, Symptom relief						
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
1 (51) [51]	Symptom relief	Progressive muscle relaxation versus placebo	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for uncertainty about how outcomes were measured
1 (72) [54]	Symptom relief	Stress management versus no stress management	4	–1	0	0	0	Moderate	Quality point deducted for sparse data

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.