Migraine headache in children

Search date June 2014

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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 questions: What are the effects of treatments for acute attacks of migraine headache in children? What are the effects of pharmacological prophylaxis for migraine headache in children? We searched: Medline, Embase, The Cochrane Library, and other important databases up to June 2014 (BMJ 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: Twenty-three studies were included. 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: 5HT1 agonists [such as triptans], non-steroidal anti-inflammatory drugs [NSAIDs], and paracetamol. And, for prophylaxis: beta-blockers, flunarizine, pizotifen, and topiramate.

QUESTIONS

INTERVENTIONS

TREATMENTS FOR ACUTE ATTACKS

Beneficial

Likely to be beneficial

PHARMACOLOGICAL PROPHYLAXIS

Unknown effectiveness

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 or NSAIDs 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 migraine headache 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 migraine headache pain at 2 hours, but not at reducing migraine recurrence within 24 hours.

  Oral rizatriptan seems to reduce nausea but we don't know if it reduces headache 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 beta-blockers as prophylaxis are more effective than placebo in preventing migraine headache in children as the evidence is weak and inconclusive.
- We don't know whether flunarizine as prophylaxis is effective at reducing migraine symptoms in children.
- Pizotifen is widely used as prophylaxis in children with migraine, but we found no trials assessing its efficacy.
- Topiramate may be useful as prophylaxis in children with migraine when compared with placebo, but the evidence is limited.

  We don’t know how prophylactic topiramate compares with prophylactic propranolol in reducing migraine headache in children as the evidence is inconsistent.

Clinical context

GENERAL BACKGROUND

Migraine is defined by the International Headache Society (IHS) as a recurrent headache that occurs with or without aura and that lasts 4 to 72 hours (2 to 72 hours in children). 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 younger than 18 years of age.

FOCUS OF THE REVIEW

The relatively high prevalence of migraine in the paediatric population, together with its attendant educational and social morbidity, mandates the clinical importance of understanding which pharmaceutical agents are available for acute treatment and prophylaxis. The evidence for the benefit of use of the most commonly used agents is presented.

COMMENTS ON EVIDENCE

There is a paucity of controlled data to support the use of most of the drugs currently recommended or licensed in the management of paediatric migraine. This has led to a tendency to extrapolate data from adult trials or to use anecdotal personal experience when considering any drug for use. The expectations for the success of treatment should take account of the level to which psychological factors are contributing to symptoms. Not all treatments work for every child, and some children will be non-responders even to those medicines for which there is the clearest evidence available from controlled trials to support their use.

SEARCH AND APPRAISAL SUMMARY

The literature search was carried out from the date of the last search, June 2010, to June 2014. For more information on the electronic databases searched and criteria applied during assessment of studies for potential relevance to the review, please see the Methods section. Searching of electronic databases retrieved 137 studies. After deduplication, 121 records were screened for inclusion in the review. Appraisal of titles and abstracts led to the exclusion of 85 studies and the further review of 36 full publications. Of the 36 full articles evaluated, two systematic reviews and three additional RCTs were included.

ADDITIONAL INFORMATION

When using pharmacological prophylaxis, avoidance of polypharmacy is probably wise. The use of each agent should be reviewed after an initial attempt at prophylaxis of around 3 months. If there has been no improvement in symptoms, consideration should be given to discontinuing it and considering an alternative. The use of long-term prophylaxis in children is probably best avoided if practical. Agents of apparent benefit to individual children should be periodically stopped (perhaps annually, taking careful account of the individual circumstances) and symptomatology reviewed to evaluate whether prophylaxis is still merited.

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 72 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 younger than 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 31). [2] Diagnosis can be more 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 EU. [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 younger than 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] From a pathophysiological perspective, central neuronal hyper-excitability may underly a susceptibility to, and the development of, migraine episodes. [12] [13] The evidence base for this suggests multifactorial causation, with amino acids, magnesium depletion, calcium channels, and controlling genes all being implicated. Once triggered, a slowly propagating wave of neuronal depolarisation,'cortical spreading dysfunction', may precipitate symptoms compounded by activation of trigeminal vascular afferents. [14] These, in turn, may sensitise other peripheral/central afferent circuits to mechanical, chemical, and thermal stimuli, with stimulation of these circuits being painful. [15] An abnormal cerebrovascular response to visual stimuli may also contribute. In support of this, people with migraine with aura exhibit a significantly higher cerebral blood flow than headache-free people in response to repetitive visual stimulation. In addition, people with migraine significantly lack habituation of this vascular response suggesting that they may have a reduced capacity to adapt to environmental stimuli (including light) and this may be part of the pathogenic process. [16] [17] The pathophysiological processes that precipitate the development of migraine in part support the logic in using calcium channel blockers therapeutically.

PROGNOSIS

We found no reliable data about the prognosis of childhood migraine headache diagnosed by IHS criteria. 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. [18] We found one longitudinal study from Sweden (73 children with 'pronounced' migraine and mean age onset of 6 years) with more than 40 years' follow-up, which predated the IHS criteria for migraine headache. [19] 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**. Migraine index is a validated scale for measuring severity in adult migraine; its validity in children is unclear.

METHODS

BMJ Clinical Evidence search and appraisal June 2014. The following databases were used to identify studies for this systematic review: Medline 1966 to June 2014, Embase 1980 to June 2014, and The Cochrane Database of Systematic Reviews 2014, issue 6 (1966 to date of issue). Additional searches were carried out in the Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment (HTA) database. We also searched for retractions of studies included in the review. Titles and abstracts identified by the initial search run by an information specialist were first assessed against predefined criteria by an evidence scanner. Full texts for potentially relevant studies were then assessed against predefined criteria by an evidence analyst. Studies selected for inclusion were discussed with an expert contributor. All data relevant to the review were then extracted by an evidence analyst. Study design criteria for inclusion in this review were published RCTs and systematic reviews of RCTs in the English language, containing 20 or more individuals (10 in each arm), of whom more than 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 3 months' 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 RCTs and systematic reviews of 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 32). 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 5HT1 AGONISTS

- For GRADE evaluation of interventions for Migraine headache in children, see table, p 32 .
- There is increasing RCT evidence that nasal sumatriptan is likely to be beneficial in reducing migraine headache 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 migraine headache pain at 2 hours, but not at reducing recurrence.
- Oral rizatriptan seems to reduce nausea, but we don't know whether it reduces headache pain when compared with placebo as the evidence is inconsistent.
- 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) with placebo. [20]

Symptom relief

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

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[20] Systematic review	Children aged <17 years 5 RCTs in this analysis	**Proportion of children with headache relief , 2 hours** 308/474 (65%) with nasal sumatriptan 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
[20] Systematic review	Children aged <17 years 4 RCTs in this analysis	**Proportion of children who were pain free , 2 hours** 144/356 (40%) with nasal sumatriptan 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. [20]

Migraine recurrence

No data from the following reference on this outcome. [20]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Taste disturbance					
[21] RCT **3-armed trial**	Children aged 12–17 years In review [20]	**Taste disturbance** 60/238 (25%) with nasal sumatriptan 20 mg 48/255 (19%) with nasal sumatriptan 5 mg 4/245 (2%) with placebo	Significance not assessed		
[22] RCT **Crossover design**	129 children, 94 included in the intention-to-treat analysis In review [20]	**Taste disturbance** 26/90 (29%) attacks with nasal 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					
[21] RCT **3-armed trial**	Children aged 12–17 years In review [20]	**Adverse effects (other than taste disturbance)** with nasal sumatriptan 20 mg with nasal sumatriptan 5 mg with placebo The study found no significant difference between groups in rates of other adverse effects		⟷	Not significant
[22] RCT **Crossover design**	129 children, 94 included in the intention-to-treat analysis In review [20]	**Adverse effects (other than taste disturbance)** with nasal 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

Rizatriptan versus placebo:

We found one systematic review (search date not reported), [20] which identified one RCT comparing oral rizatriptan with placebo. [23] We also found two subsequent RCTs comparing oral rizatriptan with placebo, [24] [25] but one of these RCTs [24] did not meet *BMJ Clinical Evidence* inclusion criteria due to high attrition (see Further information on studies).

Symptom relief

Rizatriptan compared with placebo Rizatriptan may be more effective than placebo at reducing nausea at 2 hours, but we don't know whether it is more effective than placebo at reducing headache pain at 2 hours (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[23] RCT	360 children aged 12–17 years	**Complete pain relief , at 2 hours**	P = 0.47	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	In review [20]	48/149 (32%) with rizatriptan 40/142 (28%) with placebo			
[23] RCT	360 children aged 12–17 years In review [20]	**Partial pain relief , at 2 hours** 98/149 (66%) with rizatriptan 80/142 (56%) with placebo	P = 0.08	⟷	Not significant
[25] RCT	791 children aged 6–17 years (randomised at Stage 2 following a placebo run-in period [Stage 1] – see Further information on studies)	**Pain freedom (defined as reduction in headache pain from moderate or severe to no pain on the 5-Face Pain Scale) , at 2 hours** 126/382 (33%) with rizatriptan (dosed based on weight) 94/388 (24%) with placebo Outcome assessed at 2 hours after Stage 2 of the study	OR 1.52 95% CI 1.10 to 2.10 P <0.05	●○○	rizatriptan
[25] RCT	791 children aged 6–17 years (randomised at Stage 2 following a placebo run-in period [Stage 1] – see Further information on studies)	**Pain relief (defined as reduction in headache pain from moderate or severe to mild or no pain on the 5-Face Pain Scale) , at 2 hours** 220/382 (58%) with rizatriptan (dosed based on weight) 204/388 (53%) with placebo Outcome assessed at 2 hours after Stage 2 of the study	OR 1.22 95% CI 0.91 to 1.63	⟷	Not significant
Nausea					
[25] RCT	791 children aged 6–17 years (randomised at Stage 2 following a placebo run-in period [Stage 1] – see Further information on studies)	**No nausea , at 2 hours** 329/381 (86%) with rizatriptan (dosed based on weight) 303/388 (78%) with placebo Outcome assessed at 2 hours after Stage 2 of the study	OR 1.70 95% CI 1.16 to 2.50 P <0.01	●○○	rizatriptan

Functional impairment

No data from the following reference on this outcome. [20] [23] [25]

Migraine recurrence

No data from the following reference on this outcome. [20] [23] [25]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[23] RCT	360 children aged 12–17 years In review [20]	**Adverse effects** with rizatriptan with placebo Absolute results not reported The RCT reported that one child taking rizatriptan developed transient jaundice and hyperglycaemia, which resolved within 1 week	Significance not assessed		
[25] RCT	1382 children aged 6–17 years	**Any adverse effects** 106/462 (23%) with rizatriptan (dosed based on weight) 113/515 (22%) with placebo Analysis of 'all-patients-as-treated' population, consisting of 977 children randomised who received at least one dose of study drug	Significance not assessed		
[25] RCT	1382 children aged 6–17 years	**Serious adverse effects** 0/462 (0%) with rizatriptan (dosed based on weight) 2/515 (<1%) with placebo Analysis of 'all-patients-as-treated' population, consisting of 977 children randomised who received at least one dose of study drug	Significance not assessed		

Zolmitriptan versus placebo:

We found one systematic review (search date not reported), [20] which identified one RCT comparing four interventions: oral zolmitriptan 10 mg, 5 mg, or 2.5 mg, or placebo. [26] The RCT only performed a direct comparison of zolmitriptan 10 mg with placebo. We also found two subsequent RCTs. [27] [28] The first subsequent RCT compared zolmitriptan (single dose 2.5 mg) with placebo versus ibuprofen. [27] The second subsequent RCT did not meet *BMJ Clinical Evidence* inclusion criteria (see Further information on studies). [28]

Symptom relief

Zolmitriptan compared with placebo We don't know whether oral zolmitriptan is more effective than placebo 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 12–17 years, 699 (82%) treated for at least one migraine attack In review [20]	**Proportion of children who responded (pain intensity was recorded on a 4-point scale, where 0 = no pain and 4 = severe pain) , 2 hours** 54% with zolmitriptan 10 mg 58% with placebo Absolute numbers not reported Response was defined as improvement in headache pain intensity to mild or no pain; the	Reported as not significant	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		higher response rates to placebo makes the trial results difficult to interpret The remaining arms evaluated zolmitriptan 5 mg and 2.5 mg			
[26] RCT **4-armed trial**	850 children aged 12–17 years, 699 (82%) treated for at least one migraine attack In review [20]	**Proportion of children who were pain free (pain intensity was recorded on a 4-point scale, where 0 = no pain and 4 = severe pain) , 2 hours** 25% with zolmitriptan 10 mg 20% with placebo Absolute numbers not reported The remaining arms evaluated zolmitriptan 5 mg and 2.5 mg	Reported as not significant	⟷	Not significant
[27] RCT **3-armed trial**	32 children, 29 (90%) of whom were included in the intention-to-treat analysis	**Proportion of children with pain relief (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) , 1 hour** 45% with zolmitriptan 7% with placebo Absolute numbers not reported The remaining arm evaluated ibuprofen	P <0.01 The RCT made statistical adjustments for related samples when comparing zolmitriptan versus placebo	○○○	zolmitriptan
[27] RCT **3-armed trial**	32 children, 29 (90%) of whom were included in the intention-to-treat analysis	**Proportion of children with pain relief (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) , 2 hours** 62% with zolmitriptan 28% with placebo Absolute numbers not reported The remaining arm evaluated ibuprofen	P <0.05 The RCT made statistical adjustments for related samples when comparing zolmitriptan versus placebo	○○○	zolmitriptan
[27] RCT **3-armed trial**	32 children, 29 (90%) of whom were included in the intention-to-treat analysis	**Proportion of children with pain relief (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) , 4 hours** 83% with zolmitriptan 4% with placebo Absolute numbers not reported The remaining arm evaluated ibuprofen	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. [20] [27] [26]

Migraine recurrence

No data from the following reference on this outcome. [20] [27] [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 12–17 years, 699 (82%) treated for at least one migraine attack In review [20]	**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		
[27] RCT **3-armed trial**	32 children, 29 (90%) of whom were included in the intention-to-treat analysis	**Proportion of children with adverse effects** 34% with zolmitriptan 13% with placebo Absolute numbers not reported Details of adverse effects were not reported The remaining arm evaluated ibuprofen	P <0.05	○○○	placebo

Eletriptan versus placebo:

We found one RCT comparing eletriptan with placebo. [29]

Symptom relief

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

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[29] RCT	348 children aged 12–17 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 (headache response was defined as improvement in headache pain intensity from moderate to severe at baseline to mild or no pain after treatment) , 2 hours** 80/141 (57%) with eletriptan 76/133 (57%) with placebo	P >0.05	⟷	Not significant

Functional impairment

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

Migraine recurrence

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	348 children aged 12–17 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 (including somnolence and dizziness)** 43% with eletriptan 28% with placebo Absolute numbers not reported	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 oral almotriptan (3 different doses tested) or placebo. [30] 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). [30]

Symptom relief

Almotriptan compared with placebo Oral almotriptan may be more effective than placebo at improving migraine headache pain relief at 2 hours in people 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					
[30] RCT **4-armed trial**	866 participants aged 12–17 years with a >1-year history of migraine; final analysis consisted of 714 (82%) participants who completed the study protocol	**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	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
		The remaining arms assessed oral almotriptan 12.5 mg and 25 mg See Further information on studies for subgroup analysis by age			
[30] RCT **4-armed trial**	866 participants aged 12–17 years with a >1-year history of migraine; final analysis consisted of 714 (82%) participants who completed the study protocol	**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 The remaining arms assessed oral almotriptan 6.25 mg and 25 mg 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
[30] RCT **4-armed trial**	866 participants aged 12–17 years with a >1-year history of migraine; final analysis consisted of 714 (82%) participants who completed the study protocol	**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 The remaining arms assessed oral almotriptan 6.25 mg and 12.5 mg 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
[30] RCT **4-armed trial**	866 participants aged 12–17 years with a >1-year history of migraine; final analysis consisted of 714 (82%) participants who completed the study protocol	**Proportion of participants with sustained headache relief , 2–24 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 The remaining arms assessed oral almotriptan 12.5 mg and 25 mg 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

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[30] RCT **4-armed trial**	866 participants aged 12–17 years with a >1-year history of migraine; final analysis consisted of 714 (82%) participants who completed the study protocol	**Proportion of participants with sustained headache relief , 2–24 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 The remaining arms assessed oral almotriptan 6.25 mg and 25 mg 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
[30] RCT **4-armed trial**	866 participants aged 12–17 years with a >1-year history of migraine; final analysis consisted of 714 (82%) participants who completed the study protocol	**Proportion of participants with sustained headache relief , 2–24 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 The remaining arms assessed oral almotriptan 6.25 mg and 12.5 mg 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

Almotriptan compared with placebo We don't know whether oral almotriptan is more effective than placebo 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					
[30] RCT **4-armed trial**	866 participants aged 12–17 years with a >1-year history of migraine; final analysis consisted of 714 (82%) participants who completed the study protocol	**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

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[30] RCT **4-armed trial**	866 participants aged 12–17 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. [30]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[30] RCT **4-armed trial**	866 participants aged 12–17 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 *v* placebo		

Further information on studies

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

[25] The RCT (1382 children aged 6–17 years) was conducted in two stages. Stage 1 was a double-blind placebo run-in period whereby children with migraine were randomised 20:1 to placebo or oral rizatriptan, respectively. The purpose of this stage was to identify placebo non-responders, who would then enter Stage 2. Placebo non-responders were then randomised 1:1 to oral rizatriptan (children weighing <40 kg received 5 mg dose, those 40 kg or more received 10 mg dose) or placebo at Stage 2, with randomisation stratified by age (6–11 years and 12–17 years) to define pre-pubertal and pubertal populations. The RCT found significantly greater pain freedom and no nausea at 2 hours for oral rizatriptan in children aged 12 to 17 years compared with placebo (pain freedom at 2 hours [pre-specified primary endpoint]: 87/284 [31%] with oral rizatriptan *v* 63/286 [22%] with placebo, OR 1.55, 95% CI 1.06 to 2.26, P <0.05; no nausea at 2 hours: 246/283 [87%] with oral rizatriptan *v* 224/286 [78%] with placebo, OR 1.77, 95% CI 1.13 to 2.77, P <0.05), but not for pain relief at 2 hours. The

RCT found no significant difference between the groups in children aged 6 to 11 years for these outcomes, but it was not powered for this younger age group. The trial was funded by a pharmaceutical company, and the authors were current or former employees of the company, or owned or had owned stock/stock options in the company, or had received consulting fees from the company.

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

[29] 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).

[30] The RCT reported that a pre-specified criterion for analysing all dosage groups was that almotriptan 25 mg had to be shown to be significantly better than placebo for all four primary end points (headache relief at 2 hours, nausea, photophobia, phonophobia). The 2-hour headache 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.

[30] 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 oral 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-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 migraine symptoms in children.

OPTION NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)

- For GRADE evaluation of interventions for Migraine headache in children, see table, p 32 .
- 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; [20] 2007 [31]), which identified the same two RCTs. The second review did not pool data, so we do not report it further. [31] However, the second review [31] included one further RCT [27] published subsequent to the first review, which we report separately from the original report.

Symptom relief

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

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Pain					
[20] Systematic review	Children aged <17 years 2 RCTs in this analysis	**Proportion of children with headache relief , 2 hours** 73/125 (58%) with ibuprofen 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
[20] Systematic review	Children aged <17 years 2 RCTs in this analysis	**Proportion of children who were pain free , 2 hours** 52/125 (42%) with ibuprofen 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
[27] RCT **3-armed trial**	32 children, 29 (90%) of whom were included in the intention-to-treat analysis In review [31]	**Proportion of children with pain relief , 1 hour** 45% with ibuprofen 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 The remaining arm evaluated zolmitriptan	P <0.01 The RCT made statistical adjustments for related samples when comparing ibuprofen with placebo	○○○	ibuprofen
[27] RCT **3-armed trial**	32 children, 29 (90%) of whom were included in the intention-to-treat analysis In review [31]	**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 The remaining arm evaluated zolmitriptan	P <0.05 The RCT made statistical adjustments for related samples when comparing ibuprofen with placebo	○○○	ibuprofen
[27] RCT **3-armed trial**	32 children, 29 (90%) of whom were included in the intention-to-treat analysis In review [31]	**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 The remaining arm evaluated zolmitriptan	P <0.01 The RCT made statistical adjustments for related samples when comparing ibuprofen with placebo	○○○	ibuprofen

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Nausea					
[27] RCT **3-armed trial**	32 children, 29 (90%) of whom were included in the intention-to-treat analysis In review [31]	**Proportion of children with nausea , 1 hour** 41% with ibuprofen 76% with placebo Absolute numbers not reported The remaining arm evaluated zolmitriptan	P <0.01 The RCT made statistical adjustments for related samples when comparing ibuprofen with placebo	○○○	ibuprofen
[27] RCT **3-armed trial**	32 children, 29 (90%) of whom were included in the intention-to-treat analysis In review [31]	**Proportion of children with nausea , 2 hours** 14% with ibuprofen 62% with placebo Absolute numbers not reported The remaining arm evaluated zolmitriptan	P <0.01 The RCT made statistical adjustments for related samples when comparing ibuprofen with placebo	○○○	ibuprofen

Functional impairment

No data from the following reference on this outcome. [20] [27]

Migraine recurrence

No data from the following reference on this outcome. [20] [27]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[27] RCT **3-armed trial**	32 children, 29 (90%) of whom were included in the intention-to-treat analysis In review [31]	**Proportion of children with adverse effects** 28% with ibuprofen 13% with placebo Absolute numbers not reported Adverse effects were not specified other than to state that they were primarily gastrointestinal or nervous-system related The remaining arm evaluated zolmitriptan	Reported as not significant P value not reported	⟷	Not significant

No data from the following reference on this outcome. [20]

Other NSAIDs versus placebo:

We found no RCTs.

Comment: **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. [32]

OPTION PARACETAMOL

- For GRADE evaluation of interventions for Migraine headache in children, see table, p 32 .
- We don't know whether paracetamol relieves the pain of migraine in children, as we found no RCTs that met our inclusion criteria for this review. 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 five systematic reviews (search dates not reported; [20] 2004; [33] [34] 2003; [35] 2007 [31]). All reviews identified the same single RCT, [36] which did not meet *BMJ 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

[36] 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. [32]

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

OPTION BETA-BLOCKERS

- For GRADE evaluation of interventions for Migraine headache in children, see table, p 32 .
- We don’t know whether beta-blockers as prophylaxis are more effective than placebo in preventing migraine headache in children as the evidence is weak and inconsistent.

Benefits and harms

Propranolol versus placebo:

We found one systematic review (search date 2012), [37] which identified three crossover RCTs comparing propranolol with placebo in children with migraine. [38] [39] [40] The systematic review performed a meta-analysis of the post-crossover results from the RCTs, which are reported here.

Symptom relief

Propranolol compared with placebo We don't know whether propranolol is more effective than placebo at preventing migraine headaches in children (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Symptom relief					
[37] Systematic review **Crossover design**	Children with migraine 3 RCTs in this analysis See Further information on studies	**Mean headaches per month , during 3 months** with propranolol with placebo Absolute results not reported Post-crossover results reported 171 children in this analysis (85 in the propranolol group, 86 in the placebo group)	Mean difference –1.38 95% CI –4.41 to +1.65 P value not reported Heterogeneity: I^2 = 84%, P value for heterogeneity not reported	⟷	Not significant

Functional impairment

No data from the following reference on this outcome. [37]

Migraine recurrence

No data from the following reference on this outcome. [37]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[37] Systematic review **Crossover design**	Children with migraine 3 RCTs in this analysis	**Adverse effects** with propranolol with placebo Absolute results not reported	RR 1.0 95% CI 0.51 to 1.95 P value not reported	⟷	Not significant

Timolol versus placebo:

We found one systematic review (search date 2012), [37] which identified no RCTs.

Other beta-blockers versus placebo:

We found one systematic review (search date 2012), which identified no RCTs. [37]

Propranolol versus topiramate:

We found one systematic review (search date 2012), [37] which found no RCTs comparing propanolol with topiramate. We found two subsequent RCTs comparing propranolol with topiramate as prophylaxis for migraine headache in children. [41] [42]

Symptom relief

Propranolol compared with topiramate We don't know whether propranolol is more effective than topiramate in reducing migraine headache symptoms in children, as results are inconsistent between studies (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Headache frequency					
[41] RCT	100 children aged 5–15 years with migraine headache, based on the 2nd edition on The International Classification of Headache Disorders (ICHD-II) criteria, and with frequent (at least 1 headache attack per week) or disabling headache (>20 on the PedMIDAS scale)	**Mean monthly headache frequency , after 3 months of treatment** 8.8 with propranolol 4.1 with topiramate 100 children in this analysis (50 children in each group)	P = 0.001	○○○	topiramate
[42] RCT	86 children aged 3–15 years with migraine (defined by the 2004 International Headache Society [IHS] criteria) and >3 headaches per month, or severe disabling/intolerable headache	**Mean number of headaches , at 4 months' follow-up** 1.8 with propranolol 2.3 with topiramate 78 children in this analysis (40 in the propranolol group, and 38 in the topiramate group)	P = 0.643	⟷	Not significant
Headache duration					
[41] RCT	100 children aged 5–15 years with migraine headache, based on the ICHD-II criteria, and with frequent (at least 1 headache attack per week) or disabling headache (>20 on the PedMIDAS scale)	**Mean headache duration , at 3 months** 1.35 hours with propranolol 0.56 hours with topiramate 100 children in this analysis (50 children in each group) Additional analgesic medication permitted throughout study (see Further information on studies)	P = 0.0001	○○○	topiramate
[42] RCT	86 children aged 3–15 years with migraine (defined by the 2004 IHS criteria) and >3 headaches per month, or severe disabling/intolerable headache	**Mean duration of headache attacks , at 4 months' follow-up** 2.6 with propranolol 2.2 with topiramate No further information given on unit of duration 78 children in this analysis (40 in the propranolol group, and 38 in the topiramate group)	P = 0.827	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Severity of headache					
[41] RCT	100 children aged 5–15 years with migraine headache, based on the ICHD-II criteria, and with frequent (at least 1 headache attack per week) or disabling headache (>20 on the PedMIDAS scale)	**Severity of headache (mean visual analogue scale score [from 0 = no pain to 10 = severe pain]) , at 3 months** 4.2 with propranolol 2.8 with topiramate 100 children in this analysis (50 children in each group) Additional analgesic medication permitted throughout study (see Further information on studies)	P = 0.0001	○○○	topiramate
[42] RCT	86 children aged 3–15 years with migraine (defined by the 2004 IHS criteria) and >3 headaches per month, or severe disabling/intolerable headache	**Proportion of children with headache severity affecting daily activities , at 4 months' follow-up** 6/40 (15%) with propranolol 6/38 (16%) with topiramate Headache severity not affecting daily activities reported in 34/40 children in the propranolol group, and 32/38 in the topiramate group, at 4 months' follow-up	Reported as not significant between groups at all follow-up visits P >0.05	⟷	Not significant

Functional impairment

Propranolol compared with topiramate Topiramate may be more effective than propranolol at reducing headache disability (assessed by PedMIDAS) in children, but this is based on one small study (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Headache disability					
[41] RCT	100 children aged 5–15 years with migraine headache, based on the ICHD-II criteria, and with frequent (at least 1 headache attack per week) or disabling headache (>20 on the PedMIDAS scale)	**Headache disability (assessed by PedMIDAS, whereby a score >20 = disabling) , at 3 months** 23.64 with propranolol 9.26 with topiramate PedMIDAS not fully defined 100 children in this analysis (50 children in each group) Additional analgesic medication permitted throughout study (see Further information on studies)	P = 0.001	○○○	topiramate

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

Migraine recurrence

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

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[41] RCT	100 children aged 5–15 years with migraine headache, based on the ICHD-II criteria, and with frequent (at least 1 headache attack per week) or disabling headache (>20 on the PedMIDAS scale)	**Adverse effects** with propranolol with topiramate In the propranolol group, 6% had mild hypertension, and 4% had drowsiness; in the topiramate group, 8% had hyperthermia, 6% had anorexia/weight loss, and 4% had drowsiness Adverse effects were reported as mild and transient			
[42] RCT	86 children aged 3–15 years with migraine (defined by the 2004 IHS criteria) and >3 headaches per month, or severe disabling/intolerable headache	**Adverse effects** with propranolol with topiramate RCT reported that 14% of children in the topiramate group stopped treatment due to side effects, and in the propranolol group 1 child stopped treatment due to asthma			

Propranolol versus flunarizine:

See option on Flunarizine., p 22

Further information on studies

[37] The systematic review reported significant heterogeneity among the RCTs in the meta-analysis. The authors of the review performed a sensitivity analysis, but found no variables to explain the heterogeneity. Of the three included RCTs, the first (32 children aged 7–16 years) favoured propranolol (P <0.001) for some benefit during a 3-month period, the second (53 children aged 9–15 years) favoured placebo (P <0.01) for mean headache duration, and the third (33 children aged 6–12 years) found no significant difference in mean number of headaches at 3 months. The third RCT also used a co-intervention of diet restriction in five 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). Dietary restriction may have confounded apparent treatment effects in this study. All three crossover RCTs included in the meta-analysis reported pre-crossover results.

[41] The RCT was carried out in a single site in Iran. Paracetamol and ibuprofen were permitted throughout the study for symptomatic relief of moderate to severe headache attacks (mean number of paracetamol used during follow-up: 14.22 in the propranolol group *v* 7.48 in the topiramate group; mean number of ibuprofen used during follow-up: 8.34 in the propranolol group *v* 3.26 in the topiramate group).

[42] The RCT did not provide details on allocation concealment or randomisation.

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.

Clinical guide

The paucity of robust research data renders a directive on whether to mandate the use of beta-blockers in this setting impossible. However, collective clinical experience suggests that they may be effective in some people. Given their generally good safety profile, it is reasonable to try beta-blockers provided they are avoided in children with high-risk factors such as asthma and some forms of congenital heart disease. Care should be taken to ensure consent to treatment is informed

and that realistic expectations of management are set. Some children will inevitably be non-responders though they remain at risk of developing side-effects.

OPTION FLUNARIZINE New

- For GRADE evaluation of interventions for Migraine headache in children, see table, p 32 .
- We don't know whether flunarizine as prophylaxis is more effective than placebo at reducing migraine frequency or migraine duration in children.
- We don't know how prophylactic flunarizine compares with prophylactic propranolol at reducing migraine frequency in children.

Benefits and harms

Flunarizine versus placebo:

We found two systematic reviews (search dates 2002; [43] 2012 [37]). The first systematic review [43] identified two RCTs, one parallel-group study, [44] and one crossover study. [45] The review did not perform a meta-analysis as the crossover study presented results graphically (see Further information on studies). The second systematic review [37] identified two RCTs, one of which was identified in the first systematic review (the parallel-group study). [44] The other RCT (3-armed crossover study) [46] identified in the second review was excluded by the first review as it contained a mixed population of children with migraine without aura, tension-type headaches, and mixed headaches. The second review performed a meta-analysis, which is reported here. We report an additional outcome (migraine duration) from the first review, which was not reported in the second review.

Symptom relief

Flunarizine compared with placebo We don't know whether flunarizine is more effective than placebo at reducing migraine frequency in children (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Migraine frequency					
[37] Systematic review	Children aged 18 years and younger with migraine, tension headache, and mixed headaches 2 RCTs in this analysis See Further information on studies	**Headaches per month , at 3 months** with flunarizine with placebo 127 children in this analysis (49 in the flunarizine group, 78 in the placebo group)	Mean difference –2.27 95% CI –4.65 to +0.11 P value not reported Reported as a clinically meaningful difference, but sample size in the analysis too small to be statistically significant Heterogeneity: I^2 = 85.6% (P value not reported)	⟷	Not significant
[37] Systematic review	Children aged 18 years and younger with migraine Data from 1 RCT	**Headaches per month , at 3 months** with flunarizine with placebo 42 children in this analysis	Mean difference –3.52 95% CI –4.91 to –2.13 P value not reported	○○○	flunarizine
Migraine duration					
[43] Systematic review	48 children aged 18 years or younger with migraine (defined using Vahlquist criteria) Data from 1 RCT 1 parallel-group RCT in this analysis (see Further information on studies)	**Mean headache duration per attack (hours) , at 3 months** 2.21 with flunarizine 2.76 with placebo 42 children with migraine in this analysis (21 in each group)	Standardised mean difference –0.41 95% CI –1.02 to +0.20 Reported as not statistically significant P value not reported	⟷	Not significant

Functional impairment

No data from the following reference on this outcome. [37] [43]

Migraine recurrence

No data from the following reference on this outcome. [37] [43]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[43] Systematic review	Children aged 18 years or younger with migraine 2 RCTs (1 parallel-group study and 1 crossover study) in this analysis (see Further information on studies)	**Adverse effects** with flunarizine with placebo 118 children included in this analysis The review reported that sleepiness/drowsiness and weight gain were the most commonly reported adverse events in the RCTs (see Further information on studies)			

No data from the following reference on this outcome. [37]

Flunarizine versus propranolol:

We found two systematic reviews (search dates 2002; [43] 2012 [37]), which identified the same RCT. The first systematic review reported the results of the RCT in more detail compared with the second systematic review; thus, we have reported it here.

Symptom relief

Flunarizine compared with propranolol We don't know how flunarizine and propranolol compare at improving headache frequency in children with migraine (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Migraine frequency					
[43] Systematic review	33 children aged 3–15 years with migraine (defined as episodic headaches impairing performance, plus at least 3 of: pulsating, frequently unilateral, vomiting, nausea, photophobia, visual impairment, and positive family history)	**Proportion of children with >75% improvement in headache frequency , after 4 months of treatment** 13/17 (76%) with flunarizine 12/15 (80%) with propranolol	OR 0.81 95% CI 0.15 to 4.40 Reported as not significant P value not reported	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	Data from 1 RCT				

Functional impairment

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

Migraine recurrence

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

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[43] Systematic review	33 children aged 3–15 years with migraine (defined as episodic headaches impairing performance, plus at least 3 of: pulsating, frequently unilateral, vomiting, nausea, photophobia, visual impairment, and positive family history) Data from 1 RCT	**Adverse effects** 3/17 (18%) with flunarizine 5/15 (33%) with propranolol 2 children had increased tiredness and 1 had breathlessness and difficulty concentrating in the flunarizine group; 4 children had increased tiredness and 1 had pressure behind eyes in the propranolol group; 2 children discontinued treatment because of side effects in the propranolol group	Risk difference –0.16 95% CI –0.46 to +0.14 Reported as not significant P value not reported	⟷	Not significant

Further information on studies

[37] The systematic review reported two RCTs comparing flunarizine versus placebo, [44] [46] one of which was a three-armed crossover trial (no washout period reported) with another treatment arm evaluating piracetam. [46] This RCT was also reported as having mixed population criteria; however, more than 50% of children had migraine (56 children with common migraine, 24 with tension headache, and 18 with mixed headache). Allocation concealment and blinding in the two RCTs were reported as either not adequately done or unclear.

[43] *Flunarizine compared with placebo (symptom relief)* The review reported that results of the crossover RCT (70 children aged 5–11 years with migraine) [45] were presented graphically; therefore, a quantitative analysis could not be performed. The crossover RCT was also reported to have clear crossover effect; thus, the review only reported the pre-crossover results (up to 3 months). The crossover RCT found that headache frequency (number of attacks per month) was significantly lower with flunarizine versus placebo after 2 and 3 months of treatment (P <0.001 for both time points), but there was no statistically significant difference between the two interventions at 1 month. The crossover RCT also found headache duration (number of hours per attack) was significantly lower with flunarizine versus placebo after 2 months (P <0.01) and 3 months (P <0.001) of treatment, but there was no statistically significant difference between the two interventions at 1 month.

[44] [45] In both RCTs identified by the review (parallel-group study and crossover study), symptomatic treatment with paracetamol was permitted. Randomisation, allocation concealment, and blinding were reported as either unknown or unclear for both RCTs.

[44] [45] *Flunarizine compared with placebo (adverse effects)* In the parallel-group study, [44] 3/24 (12.5%) children randomised to flunarizine withdrew due to adverse events (drowsiness, gastrointestinal complaints, fatigue); withdrawals in the placebo group were not reported. In this study, the risk difference for withdrawal due to adverse events was 0.12 (95% CI –0.03 to +0.28). In the crossover study, [45] adverse effects were not separated for flunarizine or placebo; thus, risk difference could not be calculated.

[43] *Flunarizine compared with propranolol (symptom relief)* The systematic review reported that the RCT (33 children aged 3–15 years) did not provide numerical data for headache duration and severity; thus, a quantitative analysis could not be performed for these outcomes. However, the investigators of the RCT reported a reduction in migraine severity in the propranolol group after 4 months, but not in the flunarizine group. Randomisation and blinding were reported as unknown for the RCT. The review also reported that symptomatic treatment with aspegic or alcalyl were permitted in the RCT.

Comment: Flunarizine is not currently marketed or licensed for use in the UK for migraine prophylaxis, and the studies investigating its effects are small and of poor quality.

Clinical guide
Although flunarizine is used quite widely outside the UK, given the paucity of published data it is difficult to make an objective recommendation as to the efficacy of flunarizine for use in this setting. For use in the UK it has to be imported from abroad by a licensed pharmaceutical import company under the brand name Sibelium®. It is not FDA approved for use in migraine prophylaxis in the US.

OPTION PIZOTIFEN

- For GRADE evaluation of interventions for Migraine headache in children, see table, p 32 .
- Pizotifen is widely used as prophylaxis in children with migraine, but we found no RCTs assessing its efficacy that met *BMJ Clinical Evidence* inclusion criteria.

Benefits and harms

Pizotifen versus placebo:

We found five systematic reviews (search dates 2012; [37] 2007; [47] 2004; [34] [48] 2002 [43]), all of which identified the same two RCTs, [49] [50] neither of which met *BMJ Clinical Evidence* inclusion criteria (see Further information on studies).

Further information on studies

[49] 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.

[50] 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 32 .
- Topiramate may be useful as prophylaxis in children with migraine when compared with placebo, but the evidence is limited.
- We don’t know how prophylactic topiramate compares with prophylactic propranolol in reducing migraine headache in children as the evidence is inconsistent.

Benefits and harms

Topiramate versus placebo:

We found two systematic reviews (search dates 2008; [51] 2012 [37]). The first review [51] identified two RCTs but did not perform a meta-analysis. [52] [53] The second review [37] also identified two RCTs, one of which was identified in the first review. [52] [54] The second review performed a meta-analysis, which we have reported here. We also report the RCT identified in the first review but not identified in the second review. [53] We found a subsequent RCT [55] that evaluated adverse effects from one of the RCTs identified in the second review. [54]

Symptom relief

Topiramate compared with placebo Topiramate may be more effective than placebo at reducing headache frequency in children with migraine (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Migraine frequency					
[37] Systematic review	Children with migraine 2 RCTs in this analysis One RCT in the analysis was a 3-armed trial comparing 2 doses of topiramate with placebo	**Headache frequency , per month** with topiramate with placebo Absolute results not reported At least 268 children in this analysis Placebo group was counted twice for the 3-armed study in this meta-analysis (see Further information on studies)	Mean difference –0.71 95% CI –1.19 to –0.24 P value not reported Topiramate reported as more effective than placebo	○○○	topiramate
[37] Systematic review	Children with migraine 2 RCTs in this analysis One RCT in the analysis was a 3-armed trial comparing 2 doses of topiramate with placebo	**Proportion of children with >50% reduction in headaches** with topiramate with placebo Absolute results not reported At least 268 children in this analysis Placebo group was counted twice for the 3-armed study in this meta-analysis (see Further information on studies)	RR 1.3 95% CI 0.93 to 1.84 Heterogeneity: I^2 = 50.4% P values not reported	⟷	Not significant
[53] RCT	44 children with migraine In review [51]	**Decrease in mean monthly migraine days , 4 months** 11.9 days with topiramate 5.9 days with placebo	P = 0.02	○○○	topiramate
[53] RCT	44 children with migraine In review [51]	**Proportion of children with >50% reduction in monthly migraine days , 4 months** 20/21 (95%) with topiramate 11/21 (52%) with placebo	P = 0.002	○○○	topiramate

Functional impairment

No data from the following reference on this outcome. [37] [51] [52] [53] [54]

Migraine recurrence

No data from the following reference on this outcome. [37] [51] [52] [53] [54]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[37] Systematic review	Children with migraine At least 1 RCT in this analysis	**Adverse effects** with topiramate with placebo Absolute results not reported	RR 1.53 95% CI 1.05 to 2.24 P value not reported	●○○	topiramate
[37] Systematic review	Children with migraine At least 1 RCT in this analysis	**Anorexia** with topiramate with placebo Absolute results not reported	RR 1.93 95% CI 0.76 to 4.92 P value not reported	⟷	Not significant
[37] Systematic review	Children with migraine At least 1 RCT in this analysis	**Insomnia** with topiramate with placebo Absolute results not reported	RR 1.89 95% CI 0.22 to 16.22 P value not reported	⟷	Not significant
[37] Systematic review	Children with migraine At least 1 RCT in this analysis	**Fatigue** with topiramate with placebo Absolute results not reported	RR 0.69 95% CI 0.29 to 1.62 P value not reported	⟷	Not significant
[37] Systematic review	Children with migraine At least 1 RCT in this analysis	**Dizziness** with topiramate with placebo Absolute results not reported	RR 5.30 95% CI 0.30 to 92.50 P value not reported	⟷	Not significant
[53] RCT	44 children with migraine In review [51]	**Proportion of participants who lost weight** 17/21 (81%) with topiramate 3/21 (14%) with placebo	Significance not assessed		
[53] RCT	44 children with migraine In review [51]	**Proportion of participants with lack of concentration in school** 4/21 (19%) with topiramate 0/21 (0%) with placebo	Significance not assessed		
[53] RCT	44 children with migraine In review [51]	**Proportion with paraesthesias** 5/21 (24%) with topiramate 0/21 (0%) with placebo	Significance not assessed		
[54] RCT **3-armed trial**	106 participants aged 12–17 years with at least a 6-month history of migraine In review [37]	**Proportion of participants who lost weight (<10% from baseline) , 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		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[55] RCT **3-armed trial**	106 participants aged 12–17 years with at least a 6-month history of migraine Further report of reference [54]	**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 The remaining arm assessed topiramate 50 mg daily See Further information on studies for details of tests used	P = 0.028	○○○	placebo
[55] RCT **3-armed trial**	106 participants aged 12–17 years with at least a 6-month history of migraine Further report of reference [54]	**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 The remaining arm assessed topiramate 50 mg daily See Further information on studies for details of tests used	P = 0.027	○○○	placebo
[55] RCT **3-armed trial**	106 participants aged 12–17 years with at least a 6-month history of migraine Further report of reference [54]	**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 The remaining arm assessed topiramate 50 mg daily See Further information on studies for details of tests used	P = 0.04	○○○	placebo

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

Topiramate versus propranolol:

See option on Beta-blockers: propranolol., p 17

Further information on studies

[54] *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.

[55] 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.

[37] The systematic review reported a meta-analysis of two RCTs. One of the RCTs was a three-armed trial comparing two doses of topiramate (50 mg and 100 mg) and placebo. The topiramate treatment arms have been considered separately in this analysis, both compared to the placebo group. The two RCTs identified in the review were industry sponsored.

Comment: The reviews identified several RCTs suggesting topiramate as potentially beneficial for migraine prophylaxis in population groups that included children. However, the overall evidence appears to be limited.

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.

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.

International Headache Society criteria (2013) *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

Flunarizine New option. Categorised as 'unknown effectiveness'.

5HT$_1$ agonists New RCT added. [25] Categorisation unchanged (beneficial).

Beta-blockers One systematic review [37] and two additional RCTs added. [41] [42] Categorisation unchanged (unknown effectiveness).

Pizotifen One systematic review added. [37] Categorisation unchanged (unknown effectiveness).

Topiramate One systematic review added. [37] Categorisation unchanged (unknown effectiveness).

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Competing interests: NPB declares that he has no competing interests.
We would like to acknowledge the previous contributors to this review, Guy Millman and Elizabeth James.

Disclaimer

TABLE 1 **International Headache Society criteria for migraine [1] (text in parentheses indicates suggested revisions for children under 15 years of age) [56]**

	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 4 to 72 hours (2 to 72 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) Pulsating c) Moderate to severe intensity d) Aggravated by, or causing avoidance of, routine physical activity	2.	At least 1 aura symptom that develops gradually over greater than or equal to 5 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			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?									
5 (967) [20]	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 (at least 1060) [23] [25]	Symptom relief	Rizatriptan versus placebo	4	–1	–1	–1	0	Very low	Quality point deducted for pharmaceutical-sponsored study; consistency point deducted for inconsistent results; directness point deducted for generalisability (children received initial placebo treatment)
2 (879) [26] [27]	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) [29]	Symptom relief	Eletriptan versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (866) [30]	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) [30]	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)
3 (271) [20] [27]	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
What are the effects of pharmacological prophylaxis for migraine headache in children?									
3 (171) [37]	Symptom relief	Propranolol versus placebo	4	–2	–1	–1	0	Very low	Quality points deducted for sparse data and reporting of post-crossover results; consistency point deducted for heterogeneity among studies; directness point deducted for inclusion of co-intervention
2 (178) [41] [42]	Symptom relief	Propranolol versus topiramate	4	–2	0	–2	0	Very low	Quality points deducted for sparse data, and unclear allocation concealment and randomisation in one RCT; directness points deducted for single-site study (Iran), and use of additional interventions (painkillers) in one RCT
1 (100) [41]	Functional impairment	Propranolol versus topiramate	4	–1	0	–2	0	Very low	Quality point deducted for sparse data; directness points deducted for single-site study (Iran), and use of additional interventions (painkillers) in one RCT

Important outcomes			Functional impairment, Migraine recurrence, Symptom relief						
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
3 (at least 42) [37]	Symptom relief	Flunarizine versus placebo	4	–3	0	–2	0	Very low	Quality points deducted for sparse data, crossover design RCT, and unclear randomisation, blinding, and allocation concealment; directness points deducted for inclusion of population outside our group of interest, and use of additional interventions
1 (32) [43]	Symptom relief	Flunarizine versus propranolol	4	–2	0	–2	0	Very low	Quality points deducted for sparse data, and unclear randomisation and blinding; directness points deducted for inclusion of population outside our group of interest, and use of additional interventions
3 (at least 312) [37]	Symptom relief	Topiramate versus placebo	4	–3	0	0	0	Very low	Quality points deducted for incomplete reporting of results, double reporting of placebo group in meta-analysis, and industry-sponsored studies

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.