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Drugs for the acute treatment of migraine in children and adolescents (Review)

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[Intervention Review]

Drugs for the acute treatment of migraine in children and adolescents

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ABSTRACT

Background

Numerous medications are available for the acute treatment of migraine in adults, and some have now been approved for use in children and adolescents in the ambulatory setting. A systematic review of acute treatment of migraine medication trials in children and adolescents will help clinicians make evidence-informed management choices.

Objectives

To assess the effects of pharmacological interventions by any route of administration versus placebo for migraine in children and adolescents 17 years of age or less. For the purposes of this review, children were defined as under 12 years of age and adolescents 12 to 17 years of age.

Search methods

We searched seven bibliographic databases and four clinical trial registers as well as gray literature for studies through February 2016.

Selection criteria

We included prospective randomized controlled clinical trials of children and adolescents with migraine, comparing acute symptom relieving migraine medications with placebo in the ambulatory setting.

Data collection and analysis

Two reviewers screened titles and abstracts and reviewed the full text of potentially eligible studies. Two independent reviewers extracted data for studies meeting inclusion criteria. We calculated the risk ratios (RRs) and number needed to treat for an additional beneficial outcome (NNTB) for dichotomous data. We calculated the risk difference (RD) and number needed to treat for an additional harmful outcome (NNTH) for proportions of adverse events. The percentage of pain-free patients at two hours was the primary efficacy outcome measure. We used adverse events to evaluate safety and tolerability. Secondary outcome measures included headache relief, use of rescue medication, headache recurrence, presence of nausea, and presence of vomiting. We assessed the evidence using GRADE (Grading of Recommendations Assessment, Development and Evaluation) and created 'Summary of findings' tables.

Main results

We identified a total of 27 randomized controlled trials (RCTs) of migraine symptom-relieving medications, in which 9158 children and adolescents were enrolled and 7630 (range of mean age between 8.2 and 14.7 years) received medication. Twenty-four studies focused on drugs in the triptan class, including almotriptan, eletriptan, naratriptan, rizatriptan, sumatriptan, sumatriptan + naproxen sodium, and zolmitriptan. Other medications studied included paracetamol (acetaminophen), ibuprofen, and dihydroergotamine (DHE). More than half of the studies evaluated sumatriptan. All but one study reported adverse event data. Most studies presented a low or unclear risk of bias, and the overall quality of evidence, according to GRADE criteria, was low to moderate, downgraded mostly due to imprecision and inconsistency. Ibuprofen was more effective than placebo for producing pain freedom at two hours in two small studies that included 162 children (RR 1.87, 95% confidence interval (CI) 1.15 to 3.04) with low quality evidence (due to imprecision). Paracetamol was not superior to placebo in one small study of 80 children. Triptans as a class of medication were superior to placebo in producing pain freedom in 3 studies involving 273 children (RR 1.67, 95% CI 1.06 to 2.62, NNTB 13) (moderate quality evidence) and 21 studies involving 7026 adolescents (RR 1.32, 95% CI 1.19 to 1.47, NNTB 6) (moderate quality evidence). There was no significant difference in the effect sizes between studies involving children versus adolescents. Triptans were associated with an increased risk of minor (non-serious) adverse events in adolescents (RD 0.13, 95% CI 0.08 to 0.18, NNTH 8), but studies did not report any serious adverse events. The risk of minor adverse events was not significant in children (RD 0.06, 95% CI − 0.04 to 0.17, NNTH 17). Sumatriptan plus naproxen sodium was superior to placebo in one study involving 490 adolescents (RR 3.25, 95% CI 1.78 to 5.94, NNTB 6) (moderate quality evidence). Oral dihydroergotamine was not superior to placebo in one small study involving 13 children.

Authors' conclusions

Low quality evidence from two small trials shows that ibuprofen appears to improve pain freedom for the acute treatment of children with migraine. We have only limited information on adverse events associated with ibuprofen in the trials included in this review. Triptans as a class are also effective at providing pain freedom in children and adolescents but are associated with higher rates of minor adverse events. Sumatriptan plus naproxen sodium is also effective in treating adolescents with migraine.

PLAIN LANGUAGE SUMMARY

Drugs for the acute treatment of migraine in children and adolescents

Background and review question

Migraine is a painful and debilitating disorder that is common in children (under 12 years of age) and adolescents (12 to 17 years of age). Common symptoms reported during a migraine attack are headache, nausea, vomiting, and sensitivity to light and sound. Many treatments for migraine are available, of which the most common are paracetamol (also known as acetaminophen), ibuprofen and other anti-inflammatories, and triptans. Not all triptan medications are approved for use in children or adolescents, and approvals vary from country to country.

Study characteristics

In our review, we looked at 27 randomized controlled trials of drugs compared to placebo to find out which treatments were effective at providing pain freedom two hours after treatment. We also wanted to know what side effects might be caused by the treatments. A total of 7630 children received medication in the studies. The evidence is current to February 2016. Each study had between 13 and 888 participants. Their average age was 12.9 years and ranged from 8.2 to 14.7 years. Nineteen of the studies were funded by the drug manufacturer.

Key results

Ibuprofen appears to be effective in treating children with migraine, but the evidence is limited to only two small trials. Ibuprofen is readily available and inexpensive, making it an excellent first choice for migraine treatment. Paracetamol was not shown to be effective in providing pain freedom in children, but we only found one small study. Triptans are a type of medication designed specifically to treat migraine and are often effective at providing greater pain freedom in children and adolescents. The triptans examined in children included rizatriptan and sumatriptan, while almotriptan, eletriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan were examined in adolescents. The combination of sumatriptan plus naproxen sodium is also effective at treating adolescents with migraine. Overall, there is a risk that the triptan medications may cause minor unwanted side effects like taste disturbance, nasal symptoms, dizziness, fatigue, low energy, nausea, or vomiting. The studies did not report any serious side effects.

Quality of the evidence

The overall quality of the evidence provided by the review was moderate for the triptans, but low for paracetamol and ibuprofen, as we only identified a few studies. More studies need to look at the effects of each of the migraine treatments in children and adolescents separately.

SUMMARY OF FINDINGS

Summary of findings 1. Should ibuprofen be used to treat children with migraine?

Ibuprofen compared with placebo in children with migraine

Patient or population: acute treatment of migraine in children
Setting: ambulatory
Intervention: ibuprofen
Comparison: placebo

Outcomes	Anticipated absolute effects[a] (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Response with placebo	Response with Ibuprofen			
Pain freedom at 2 h	Study population		RR 1.87 (1.15 to 3.04)	125 (2 RCTs)	⊕⊕◯◯[b,c] Low
	267 per 1000	499 per 1000 (307 to 811)			
Adverse events	100 per 1000	0 per 1000 (− 13 to 13)	RD 0.00 (− 0.13 to 0.13)	80 (1 RCT)	

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

CI: confidence interval; **RR**: risk ratio; **RD**: risk difference

[a]The response in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
[b]In the two studies, there were no serious risks of bias, inconsistency, indirectness, or publication bias. We downgraded quality of evidence by two levels due to very serious imprecision (small sample size, few events, and wide confidence interval).
[c]High (⊕⊕⊕⊕) = further research is very unlikely to change our confidence in the estimate of effect; Moderate (⊕⊕⊕◯) = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; Low (⊕⊕◯◯) = 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; Very Low (⊕◯◯◯) = any estimate of effect is very uncertain.

Summary of findings 2. Should triptans be used to treat children with migraine?

Triptans compared with placebo in children with migraine

Patient or population: acute treatment of migraine in children
Setting: ambulatory
Intervention: triptans
Comparison: placebo

Outcomes	Anticipated absolute effects[a] (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Response with placebo	Response with triptans				
Pain freedom at 2 h	Study population		RR 1.67 (1.06 to 2.62)	345 (3 RCTs)	⊕⊕⊕◯[b,c] MODERATE	Includes rizatriptan oral (1 study) and sumatriptan by nasal spray (2 studies)
	276 per 1000	461 per 1000 (292 to 723)				
Adverse events	176 per 1000	11 per 1000 (− 7 to 30)	RD 0.06 (− 0.04 to 0.17)	420 (3 RCTs)		

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

CI: confidence interval; **RR**: risk ratio; **RD**: risk difference.

[a]The response in the intervention group (and its 95% confidence interval) is based on the assumed response in the comparison group and the **relative effect** of the intervention (and its 95% CI).
[b]In the three studies, there were no serious risks of bias, inconsistency, indirectness, or publication bias detected. Quality of evidence was downgraded by one level due to serious imprecision (small sample size, few events, and wide confidence interval).
[c]High (⊕⊕⊕⊕) = further research is very unlikely to change our confidence in the estimate of effect; Moderate (⊕⊕⊕◯) = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; Low (⊕⊕◯◯) = 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; Very Low (⊕◯◯◯) = any estimate of effect is very uncertain.

Summary of findings 3. Should triptans be used to treat adolescents with migraine?

Triptans compared with placebo in adolescents with migraine

Patient or population: acute treatment of migraine in adolescents
Setting: ambulatory
Intervention: Triptans
Comparison: placebo

Outcomes	Anticipated absolute effects[a] (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Response with placebo	Response with Triptans				
Pain freedom at 2 h	Study population		RR 1.32 (1.19 to 1.47)	6761 (21 RCTs)	⊕⊕⊕◯[b,c] MODERATE	Includes almotriptan (1 study), eletriptan (1 study), naratriptan (1 study), rizatriptan (4 studies), sumatriptan (10 studies), and zolmitriptan (4 studies)
	230 per 1000	303 per 1000 (273 to 338)				
Adverse events	184 per 1000	24 per 1000 (15 to 33)	RD 0.13 (0.08 to 0.18)	7876 (21 RCTs)		

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

CI: confidence interval; **RR**: risk ratio; **RD**: risk difference.

[a]The response in the intervention group (and its 95% confidence interval) is based on the assumed response in the comparison group and the **relative effect** of the intervention (and its 95% CI).
[b]Serious inconsistency was observed in the effect estimates. All of the triptans with only 1 study were not statistically superior to placebo (i.e. almotriptan, eletriptan, naratriptan) in producing pain freedom while the three triptans with 2 or more studies (i.e. rizatriptan, sumatriptan, and zolmitriptan) were statistically significant with a higher magnitude of effect. In the subgroup analysis of the individual triptan groups through, the subgroup differences were not statistically significant (P = 0.45).
[c]High (⊕⊕⊕⊕) = further research is very unlikely to change our confidence in the estimate of effect; Moderate (⊕⊕⊕◯) = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; Low (⊕⊕◯◯) = 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; Very Low (⊕◯◯◯) = any estimate of effect is very uncertain.

Summary of findings 4. Should sumatriptan plus naproxen sodium be used to treat adolescents with migraine?

Sumatriptan + naproxen sodium compared with placebo in adolescents with migraine

Patient or population: acute treatment of migraine in adolescents
Setting: ambulatory

Intervention: sumatriptan + naproxen sodium
Comparison: placebo

Outcomes	Anticipated absolute effects[a] (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Response with placebo	Response with Sumatriptan + naproxen sodium				
Pain freedom at 2 h	Study population		RR 2.66 (1.57 to 4.51)	485 (1 RCT)	⊕⊕⊕○[b,c] MODERATE	Doses including sumatriptan + naproxen 10 mg + 60 mg, 30 mg + 180 mg, and 85 mg + 500 mg were all well tolerated and demonstrated similar efficacy
	99 per 1000	262 per 1000 (163 to 394)				
Adverse events	83 per 1000	2 per 1000 (− 2 to 7)	RD 0.03 (− 0.02 to 0.09)	490 (1 RCT)		

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

CI: confidence interval; **RR**: risk ratio; **RD**: risk difference.

[a]The response in the intervention group (and its 95% confidence interval) is based on the assumed response in the comparison group and the **relative effect** of the intervention (and its 95% CI).
[b]The confidence interval of the effect size is wide. The true effect may be substantially different than the estimated effect in producing pain freedom.
[c]High (⊕⊕⊕⊕) = further research is very unlikely to change our confidence in the estimate of effect; Moderate (⊕⊕⊕○) = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; Low (⊕⊕○○) = 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; Very Low (⊕○○○) = any estimate of effect is very uncertain.

BACKGROUND

Migraine is a common and disabling disease, affecting 3% to 10% of children and adolescents (Stovner 2007). Children as young as two years of age may be affected, and most adults with migraine have their first headache in early childhood or adolescence (Bille 1997). Quality-of-life studies indicate that migraine has a significant negative impact on a child (Powers 2003; Powers 2004). Indeed, migraines can be a tremendous source of anxiety for children, adolescents, and their parents, disrupting both school obligations and parental work responsibilities. These concerns may be amplified when there is uncertainty on the physician's part as to the best treatment.

The International Classification of Headache Disorders, 3rd edition, beta version (ICHD-3 beta), provides the most accepted and current definition of migraine. The presence of headache, often associated with nausea, vomiting, or both is common to adults, adolescents, and children with migraine. However, the criteria acknowledge that children and adolescents' migraines may be shorter but will last at least two hours, and the pain may be bilateral over the frontotemporal head regions or non-pulsatile. Adolescents, like adults, will usually begin to report unilateral pulsatile pain. The presence of photophobia and phonophobia may need to be inferred from behaviour such as a preference for a quiet and dimly lit room during a migraine attack.

Treatments for migraine include symptom-relieving and preventive strategies. Preventive medications are used to reduce the frequency and severity of migraine attacks. Symptom-relieving therapies commonly aim to eliminate head pain and reduce the symptoms associated with migraine, including nausea, phonophobia, and photophobia. Oral analgesics such as paracetamol and ibuprofen are the mainstay of acute therapy for migraine in children and adolescents (Hämäläinen 2002). However, other agents such as ergot derivatives (e.g. dihydroergotamine) and the serotonin 1b/1d receptor agonists (triptans) have demonstrated efficacy in adults. Many of these medications have now been studied in children and adolescents, and some are approved for use in the pediatric age group. A practice parameter on this topic has been published by the American Academy of Neurology Quality Standards Subcommittee and the Practice Committee of the Child Neurology Society (Lewis 2004). This systematic review will summarize and update the evidence base and provide a meta-analysis of the data.

OBJECTIVES

To assess the effects of pharmacological interventions by any route of administration versus placebo for migraine in children and adolescents 17 years of age or less. For the purposes of this review, children were defined as under 12 years of age and adolescents 12 to 17 years of age.

METHODS

Criteria for considering studies for this review

Types of studies

We included all prospective, placebo-controlled trials of pharmacological interventions for symptomatic or acute treatment of migraine in children and adolescents in the outpatient setting if allocation to treatment groups was randomized (see Differences between protocol and review). We included studies regardless of design (i.e. parallel-group or cross-over), publication status, or language of publication. We included cross-over studies, as migraine is an episodic disorder, and we did not expect any carry-over or period effects (see Differences between protocol and review). We excluded non-placebo-controlled studies, concurrent cohort comparisons and other quasi- or non-experimental designs.

Types of participants

We included studies involving pediatric participants 17 years of age or less with a diagnosis of migraine with or without aura. For the purposes of the review, we defined children as under 12 years of age and adolescents as 12 to 17 years of age (see Differences between protocol and review). We recorded inclusion age criteria, including median and mean age of subjects. We excluded studies involving both pediatric and adult patients unless they reported results separately for the pediatric patients. We analyzed separately the data from studies that included both children and adolescents when possible. If studies did not report the data separately, we used the mean age as a surrogate. If the mean age in the study was less than 12 years, we considered the study population to be of predominantly childhood age. If the mean age was greater than or equal to 12 years, we considered the study population to be of predominantly adolescent age.

Migraine is defined by clinical symptoms and signs in the 3rd edition of the International Classification of Headache Disorders, beta version (ICHD-3 beta). ICHD-3 beta includes revised comments for the diagnosis of migraine in children and adolescents, including shorter duration of headache (2 to 72 hours), bilateral frontotemporal location, and the presence of photophobia and phonophobia as inferred from behaviour. There have been two other versions of the International Classification of Headache Disorder and a proposed revision of the 1988 criteria in the context of children or adolescents (IHS 1988; ICHD-2; Winner 1995). We included a study in this review if investigators used any version of the International Headache Society classification systems above or the proposed revision for pediatrics for the diagnosis of migraine with or without aura.

Types of interventions

We included studies allocating participants to receive a pharmacological intervention by any route of administration for symptomatic acute treatment of a migraine attack. Acceptable comparator groups included placebo or other active drug treatments. We identified the use of preventive medication and examined this in subgroup analysis, but discontinuation was not required for inclusion.

Types of outcome measures

We chose outcomes to assess both efficacy and safety. We selected the primary efficacy outcome based on the suggested guidelines for controlled trials of drugs in migraine (Tfelt-Hansen 2012). The primary outcome for safety was based on the report of adverse events. All outcome measures were reported for the treatment of a single attack (see Differences between protocol and review).

Primary outcomes

The primary outcome measure for efficacy was the percentage of pain-free participants at two hours; we defined pain freedom as the absence of pain at two hours before the use of additional or

rescue medication (see Differences between protocol and review). Headache relief is a frequently used primary outcome measure that is variably defined based on the scale used to assess pain. For example, if using the four level scale of none, mild, moderate, or severe pain, investigators or physicians may define headache relief as a decrease in pain from moderate or severe to mild or none. Some in the migraine research community have challenged the use of headache relief as a primary outcome measure; for example, migraine sufferers generally do not consider headache relief a success and expect pain freedom from an intervention (Davies 2000; Lipton 2002). Given these considerations, we classified headache relief as a secondary outcome measure (see Differences between protocol and review).

We used the percentage of participants with any adverse event(s) as the primary safety outcome measure, and this was required for inclusion in the analysis (see Differences between protocol and review). We defined adverse events as any unwanted effect that occurred during treatment. We also documented the proportion of participants reporting any serious adverse events when possible. Serious adverse events included death, any life-threatening condition, hospitalization, disability or permanent damage, required intervention to prevent permanent damage, or any other important medical event that could jeopardize the participant or require medical or surgical intervention.

Some aspects of the original protocol were not necessary to implement given the way studies reported outcome data. We document these considerations in the Differences between protocol and review section.

Secondary outcomes

We assessed the following secondary outcome measures.

- Headache relief (headache response): the percentage of participants with headache relief at two hours is typically defined as a decrease in headache intensity from severe or moderate to mild or none at two hours prior to the use of rescue medication. When studies used alternate definitions of pain intensity (e.g. numerical scale), they needed to describe a level of relief that would be meaningful to a participant and to reflect a decrease in headache intensity similar to that assumed in the above definition.
- Rescue medication: the percentage of participants taking rescue medication at two hours or earlier to a maximum of six hours after the test drug. The definition of rescue medication was variable and often included any use of medication to treat the recurrence of headache within a specified timeframe (i.e. usually 24 hours). For the purposes of the review, rescue medication was defined as the use of any medication between 2 and 24 hours.
- Headache recurrence: the percentage of participants who were initially pain-free or achieved the study primary outcome of headache relief within 2 hours without the use of rescue medication but who experienced recurrence of any headache from 2 to 48 hours.
- Presence of nausea: percentage of participants with nausea at two hours after taking the test drug.
- Presence of vomiting: percentage of participants with vomiting within two hours of taking the test drug.

We did not include participant preference, presence of photophobia, or presence of phonophobia in the analysis as originally planned in the protocol (see Differences between protocol and review).

Search methods for identification of studies

We conducted a search of electronic databases in collaboration with a research librarian using search strategies to identify the highest level of evidence for the topic. In addition, we manually searched other sources listed below.

Electronic searches

We systematically searched the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL) (1991 to 2013, Issue 3).
- OvidSP MEDLINE (1946 to February 2016).
- Ovid MEDLINE In-Process & Other Non-Indexed Citations (2012 to February 2016).
- EMBASE (1980 to February 2016).
- Database of Abstracts and Reviews of Effects (1991 to April 2013).
- International Pharmaceutical Abstracts (1970 to April 2013).
- PsycINFO (1806 to April 2013).
- EBSCOhost CINAHL (Cumulative Index of Nursing and Allied Health) (1937 to April 2013).

The search strategies used a combination of text words and medical subject headings (MeSH), adapted for each database searched: concepts included migraine, headache, cephalgia or cephalalgia, drug therapy, drug treatment, antimigraine therapy, antimigraine treatment, and treatment outcome, combined with drugs and acute treatments known to be used for migraine in children and adolescents. These terms were combined with a pediatric filter designed by the librarian (Lisa Tjosvold) of the Cochrane Child Health Field.

Complete search strategies are given in Appendix 1.

Searching other resources

We conducted a gray literature search including reviewing the reference lists of included studies and handsearching meeting abstracts from the American Headache Society and International Headache Society Scientific meetings. The review authors attempted to contact primary authors, experts in the area, and drug manufacturers (GlaxoSmithKline, AstraZeneca, Ortho-McNeil, Merck, and Pfizer) for information on recent, ongoing, or unpublished trials. We searched ClinicalTrials.gov for new or ongoing studies and used Current Controlled Trials (www.controlled-trials.com) to search across multiple trial registries. GlaxoSmithKline (www.gsk-clinicalstudyregister.com) and AstraZeneca (www.astrazenecaclinicaltrials.com) have clinical trial registries and report on both published and unpublished studies.

Data collection and analysis

Selection of studies

We identified potentially relevant articles by reviewing the titles and abstracts from the original search. We considered studies with insufficient information in the title or abstract as potentially relevant articles for further assessment. We then reviewed the full text of potentially relevant studies for inclusion or exclusion.

Two reviewers independently carried out both steps. A third, independent reviewer resolved any disagreements that arose between them.

Data extraction and management

One reviewer used a standardized data abstraction form to extract data, which a second reviewer then checked for accuracy and completeness. We recorded extracted data in Review Manager 5 (RevMan 2014). A third, independent reviewer resolved discrepancies.

Assessment of risk of bias in included studies

Two reviewers assessed risk of bias using the 'Risk of bias' table for each study. Reviewers assessed five domains before making a judgement: sequence generation, allocation concealment, blinding, incomplete outcome data, and selective reporting (Higgins 2011). We resolved any disagreements by discussion. We did not use the Jadad scale as planned in the protocol, as per current recommendations of the Cochrane Collaboration (Differences between protocol and review).

Assessment of quality of evidence in included studies

We assessed the overall quality of the evidence for each outcome using the GRADE system and included our assessment in the 'Summary of findings' tables in order to present the main findings of the review in a transparent and simple tabular format (GRADEPro 2015). In particular, we included key information concerning the quality of evidence, the magnitude of effect of the interventions examined, and the sum of available data on the main outcomes.

The GRADE system uses the following criteria for assigning a level of evidence.

- High: further research is very unlikely to change our confidence in the estimate of effect.
- Moderate: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low: 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.
- Very low: any estimate of effect is very uncertain.

We decreased the grade if we found:

- serious (− 1) or very serious (− 2) limitations to study quality;
- important inconsistency(s) (− 1);
- some (− 1) or major (− 2) uncertainty about directness;
- imprecise or sparse data (− 1);
- high probability of reporting bias (− 1).

'Summary of findings' table

We decided *post hoc* to include four 'Summary of findings' tables to present the main findings in a transparent and simple tabular format. In particular, we included key information concerning the quality of evidence, the magnitude of effect of the interventions examined, and the sum of available data on the outcomes pain freedom at 2 hours and adverse events, for the four main comparisons.

Measures of treatment effect

We reported the risk ratio (RR) for all primary and secondary efficacy outcome measures with 95% confidence intervals (CIs) as well as the number needed to treat for an additional beneficial outcome (NNTB). We reported the risk difference (RD) with 95% CIs for the adverse events as the primary measure of harm as well as the number needed to treat for an additional harmful outcome (NNTH).

Unit of analysis issues

We included cross-over trials with binary outcomes in the analysis (Curtin 2002). None of the cross-over trials reported any significant carry-over or period effects, and none would be expected based on the acute episodic nature of migraine.

Dealing with missing data

We only analyzed the available data for all outcomes. We assessed the possibility of missing studies as described below (see Assessment of reporting biases). We considered variability in the reporting of outcomes to be random.

Assessment of heterogeneity

We assessed heterogeneity using the I^2 statistic. We interpreted the I^2 statistic as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Assessment of reporting biases

We assessed reporting biases qualitatively by visually examining the funnel plot and quantitatively using a modified version of Egger's test (Egger 1997; Harbord 2006), as implemented in the metabias module for Stata statistical software package on the triptan versus placebo studies in adolescents using the pain-free outcome (Stata 14).

Data synthesis

We pooled studies using a Mantel-Haenszel, random-effects model. We pooled dichotomous outcomes, and calculated RRs with 95% CIs. We calculated the number needed to treat for an additional beneficial outcome (NNTB) for RRs of the primary outcome that were statistically significant. For adverse events, we combined data combined using RDs with 95% CIs. We calculated the number needed to treat for an additional harmful outcome (NNTH) for RDs of adverse events that were statistically significant. We included studies with small sample sizes and imprecise effect estimates, but we graded them lower for quality and weighted them accordingly in the meta-analyses.

We combined trials of cross-over design with parallel group trials in the meta-analysis. We included outcome measures from each intervention period in the analysis as if the trial were a parallel group trial. We also included three-way cross-over studies with two intervention periods and one placebo period as if they were a parallel group trial, but we divided the placebo period in two to avoid double counting the placebo interventions. Paired analysis was not possible for any of the included studies (see Differences between protocol and review). This method of including cross-over studies will tend to produce wider confidence intervals and is considered a more conservative assessment of treatment effect given that these studies will receive a lower weight in the meta-analyses. We included study design in the sensitivity analysis to assess the influence of cross-over design on our final conclusions.

Subgroup analysis and investigation of heterogeneity

We used the I^2 statistic to determine the presence of heterogeneity and test for subgroup differences as implemented in RevMan, used to prepare this review (Higgins 2002; RevMan 2014). We performed all subgroup analyses for the pain-free outcome measure using the placebo-controlled studies of triptan medications versus placebo in adolescents (except for the age-based subgroup analysis).

Post hoc subgroup analyses included the following.

1. Intranasal route.
2. Preventive medication permitted during the study.

Sensitivity analysis

We examined potential sources of heterogeneity using the following a priori sensitivity analyses (see Differences between protocol and review).

1. Allocation concealment (low, unclear, or high risk of bias).
2. Cross-over versus parallel-group study design.
3. Source of funding (pharmaceutical, non-pharmaceutical, or unclear).
4. Reported in a peer-reviewed indexed journal.
5. Small sample size ≤ 50.

We performed all sensitivity analyses for the pain-free primary outcome using the studies of triptan medications versus placebo in adolescents.

RESULTS

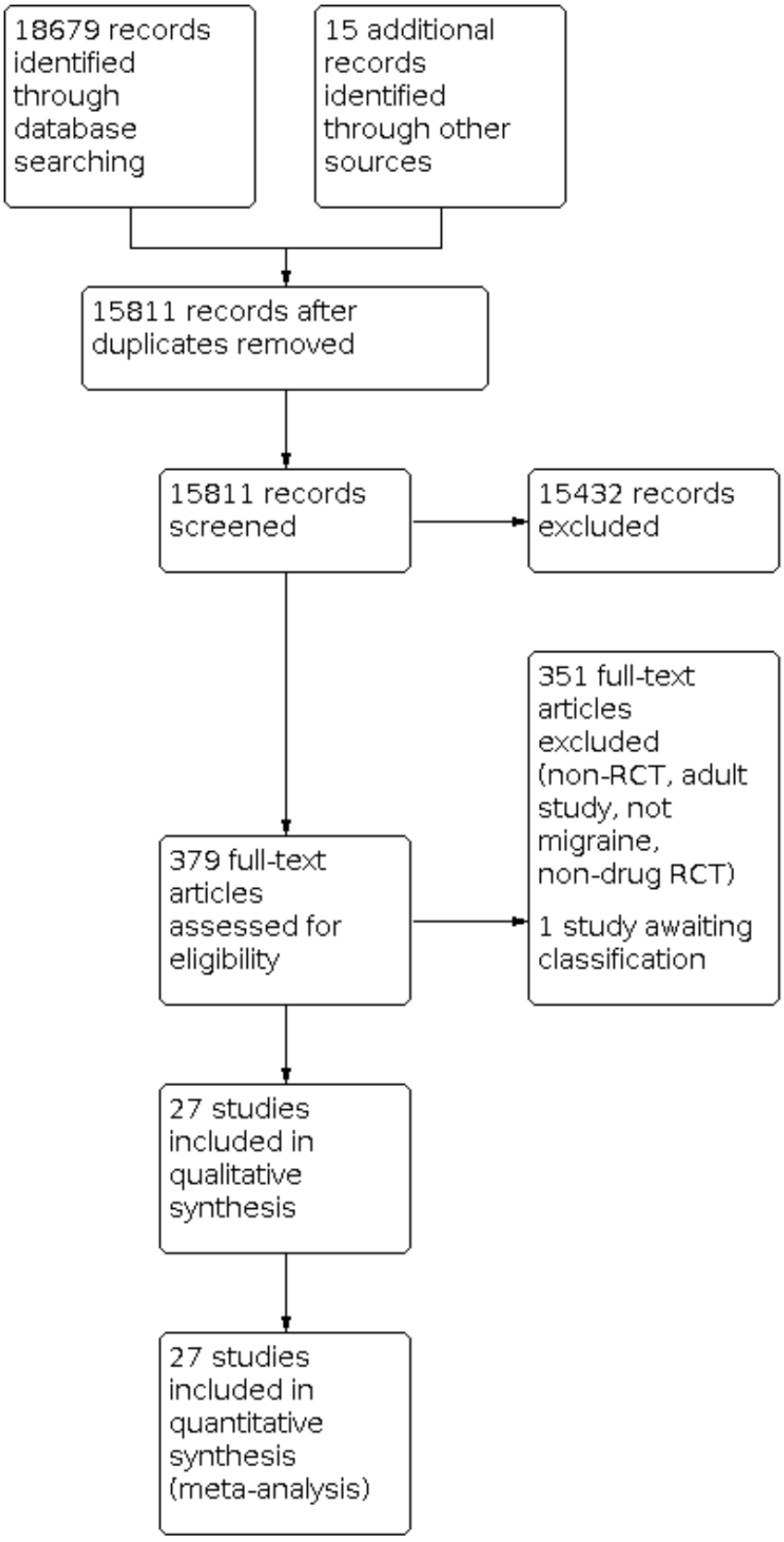
Description of studies

See Characteristics of included studies, Characteristics of excluded studies, Characteristics of ongoing studies.

Results of the search

The literature search and review of the gray literature yielded 15,811 unique citations, 379 of which we assessed as full-text articles for eligibility. Some of our data requests to manufacturers were met with referrals to trial registry websites or data were not made available. A total of 27 randomized placebo-controlled trials of acute drug therapy for migraine met our inclusion criteria (Figure 1).

Figure 1. Study flow diagram.



Included studies

The mean age of inclusion was 12.9 years with a range of means between 8.2 and 14.7 years. The minimum age of inclusion was 4 years in one study (Hämäläinen 1997a), and the maximum age for inclusion was 18 years in two studies (Evers 2006; Hämäläinen 1997b). Three studies included only children under 12 (Hämäläinen 2002; Lewis 2002; Ueberall 1999), and one study reported data for children and adolescents separately (Ho 2012). Six studies included children and adolescents, but they did not report the data separately (Ahonen 2004; Ahonen 2006; Evers 2006; Hämäläinen 1997a; Hämäläinen 1997b; Hämäläinen 1997c). Participants in two of the studies reporting children and adolescents combined had a mean age of less than 12 years and were included in the analysis as studies of predominantly children (Hämäläinen 1997a; Hämäläinen 1997c). Participants in the remaining four studies where children and adolescents were combined had a mean age of greater than 12 years, and we considered them to be studies of predominantly adolescents for the analysis. Finally, 17 studies included only adolescents over the age of 12 years (Callenbach 2007; Derosier 2012; Fujita 2014; Lewis 2007; Linder 2008; NCT01211145; Rothner 1997; Rothner 1999a; Rothner 1999b; Rothner 1999c; Rothner 2006; Visser 2004a; Winner 1997; Winner 2000; Winner 2002; Winner 2006; Winner 2007). The mean number of participants randomized was 359 with a range of 13 to 888. We summarize the characteristics of included studies in Table 1, and we summarize the individual studies in Table 2. We provide more details, including a risk of bias assessment, in Characteristics of included studies.

Excluded studies

We excluded two studies, one that compared intravenous prochlorperazine versus ketorolac in children and adolescents presenting to the Emergency Department (ED) (Brousseau 2004) and one that compared intravenous metoclopramide to placebo in children and adolescents presenting to the ED (NCT00355394) from the analysis as our review is focused on outpatient acute drug therapy. All other excluded studies were either not controlled or were non-drug clinical trials (see Characteristics of excluded studies).

Awaiting classification

A single study was recently published and is awaiting classification (Winner 2015). It is a cross-over study of sumatriptan + naproxen sodium in adolescents (see Characteristics of studies awaiting classification).

Risk of bias in included studies

We illustrated the risk of bias in included studies in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

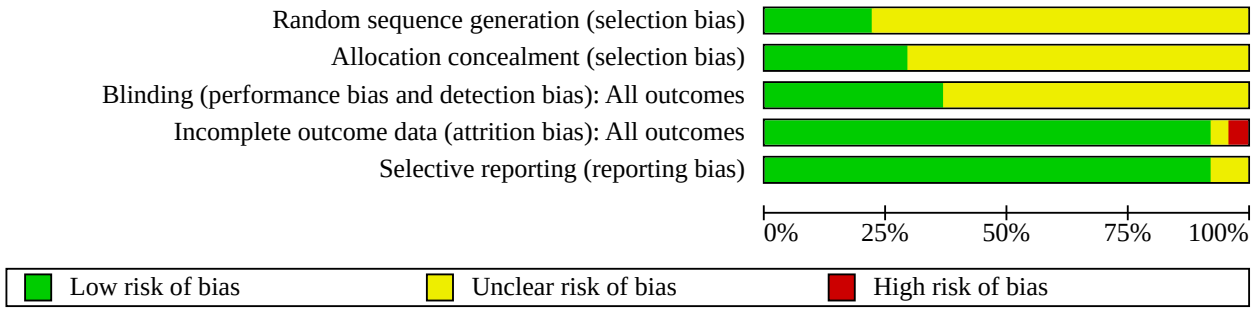


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

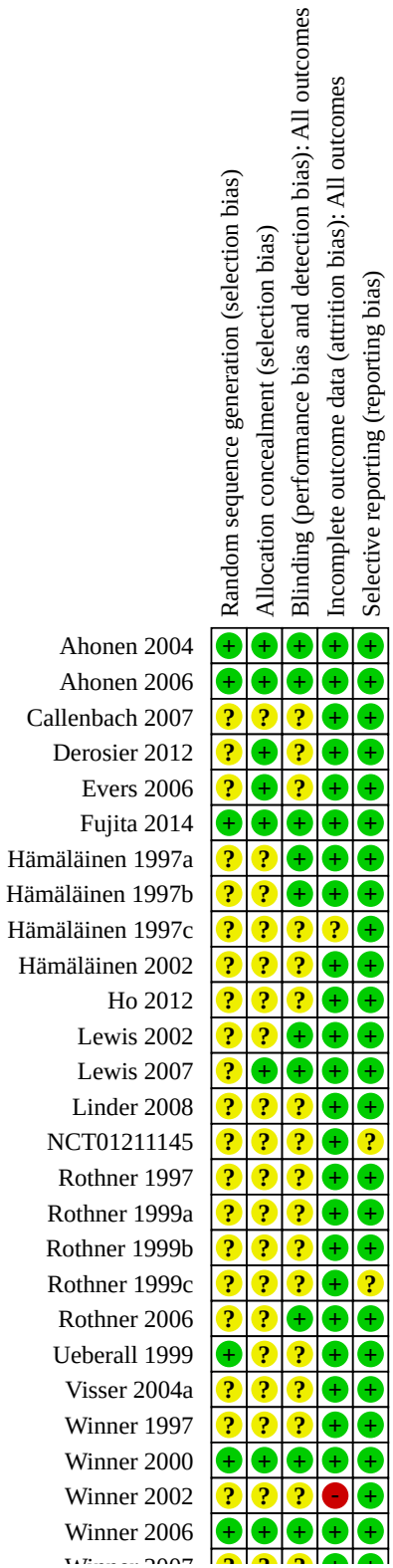
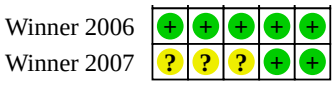


Figure 3. (Continued)



Allocation

Investigators described all studies as randomized (low risk of selection bias (random sequence generation)), but the method of randomization was unclear in 19 studies (unclear risk of bias). Authors frequently employed generic descriptions of sequence generation such as 'randomized 1:1' or 'block randomization to two age groups'. Eight studies adequately reported allocation concealment, and we judged them to be at low risk of selection bias (allocation concealment). We judged the remaining 19 studies to be at unclear risk of bias for this domain.

Blinding

Generally, authors described all studies as double-blind, but 17 studies did not report their methods for blinding clearly (unclear risk of bias). All studies were either an oral or intranasal medication compared with placebo. Studies seldom described efforts to match for taste, color, smell, etc. We considered 10 studies to be at low risk of bias.

Incomplete outcome data

We considered incomplete reporting of outcome data to confer a high risk of bias in Winner 2002 and an unclear risk in Hämäläinen 1997c. We considered the remaining 25 studies to be at low risk.

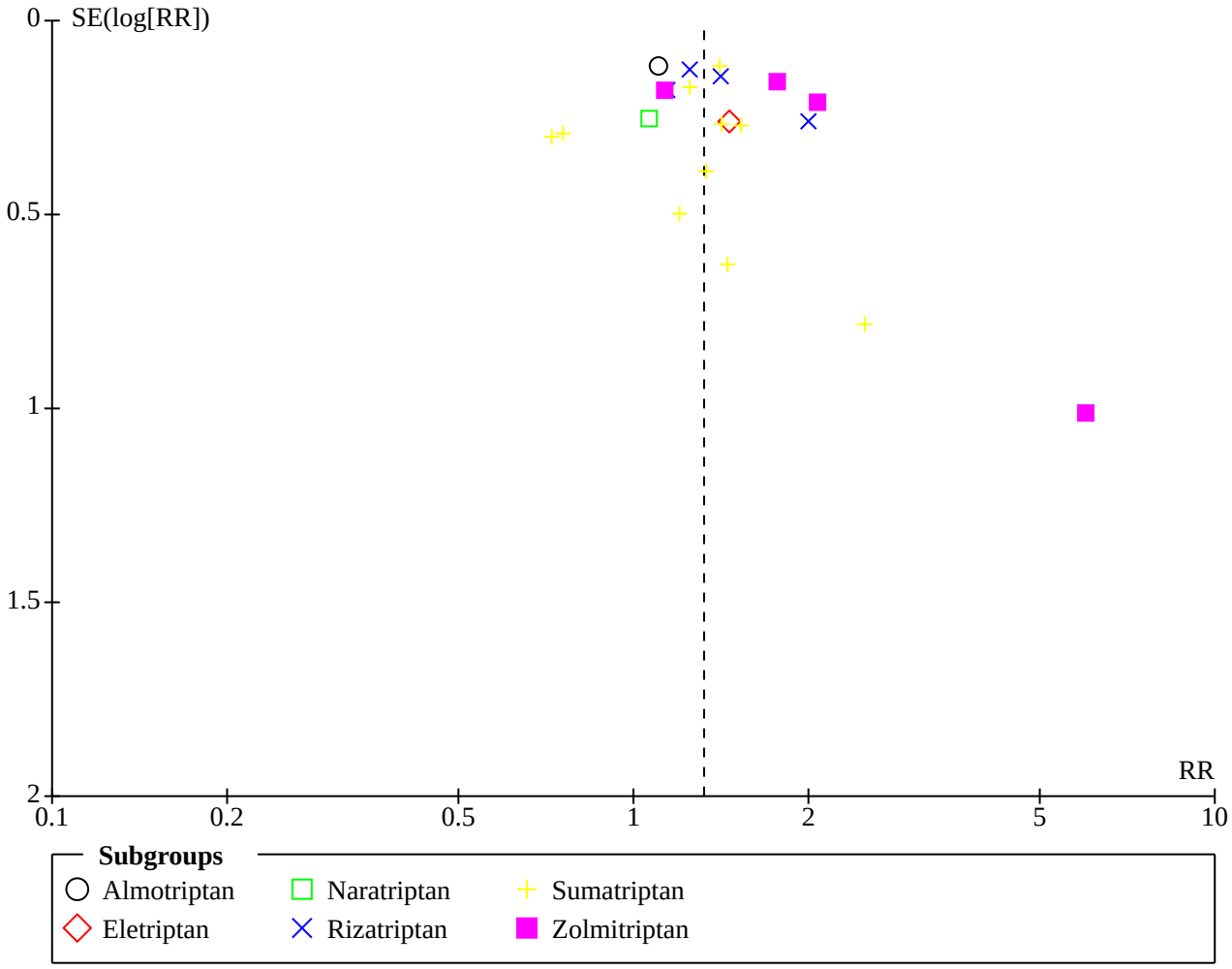
Selective reporting

Six studies were reported only in the sponsors' clinical trial report registry and published only in abstract form (Hämäläinen 2002; Rothner 1997; Rothner 1999a; Rothner 1999b; Rothner 1999c; Winner 1997), while one study was reported only in the sponsor's clinical trial report registry (NCT01211145). All included studies reported the pain-free primary efficacy outcome. The reports available through the sponsors' clinical trial registries were comprehensive in reporting all planned outcome measures and greatly enhanced the reported data that was published in abstract form. Also, there were no discrepancies between published abstracts and the reports released through the sponsor's clinical trial registry. Derosier 2012 was the only study that did not report the headache relief secondary outcome, and Lewis 2002 did not report adverse event data; we judged these two studies to be at unclear risk of bias for this domain. We judged the remaining 25 studies to be at low risk of bias.

Other potential sources of bias

We assessed publication bias based on the pain-free outcome for all triptans versus placebo in adolescents. On visual inspection, the funnel plot showed some asymmetry (Figure 4), suggesting the possibility of publication or other sources of bias and small-study effects. We used Egger's test to explore small-study effects, which were not significant (P = 0.139). The inclusion of published and unpublished data from the clinical trial registries would suggest a reduced risk of publication bias, as many of these studies were negative.

Figure 4. Funnel plot of comparison: 7 Triptans vs placebo in Adolescents, outcome: 7.1 Pain-free.



Effects of interventions

See: **Summary of findings 1** Should ibuprofen be used to treat children with migraine?; **Summary of findings 2** Should triptans be used to treat children with migraine?; **Summary of findings 3** Should triptans be used to treat adolescents with migraine?; **Summary of findings 4** Should sumatriptan plus naproxen sodium be used to treat adolescents with migraine?

We describe the measures of effect for each of the interventions below. In addition, we present 'Summary of findings' tables for all comparisons for which there was more than one study.

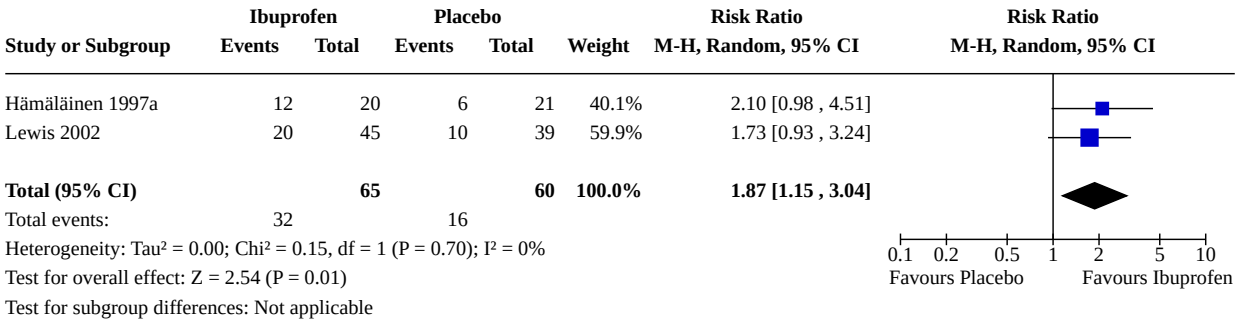
Paracetamol versus placebo in children

In the one three-way cross-over study that evaluated paracetamol (Hämäläinen 1997a), the participant age ranged from 4 to 15.8 years (N = 88), but investigators did not report results for children and adolescents separately. However, the mean age of inclusion was 10.7 years, so we deemed the study to be predominantly in children. Paracetamol was not superior to placebo for the pain-free outcome (RR 1.40, 95% CI 0.75 to 2.58). There was no statistically significant difference in headache relief (defined as a reduction in pain by two grades on a five point scale), rescue medication, headache recurrence, or adverse events. The study did not report the presence of nausea or vomiting.

Ibuprofen versus placebo in children

Ibuprofen was superior to placebo in the pooled analysis of two studies (Figure 5) - Hämäläinen 1997a was a three-way cross-over study with paracetamol, with a mean participant age of 10.7 years (N = 88), and Lewis 2002 was a parallel group study that included only 6 to 12 year-olds with a mean age of 9 years (N = 84). For the pain-free primary outcome, the RR was 1.87 (95% CI 1.15 to 3.04; Analysis 1.1) with a NNTB of 4. Ibuprofen was also superior to placebo for headache relief (Analysis 1.3) but not for rescue medication (Analysis 1.4) or headache recurrence (Analysis 1.5). There was no difference in the proportion of adverse events between groups (Analysis 1.2). Lewis 2002 did not report adverse events, and Hämäläinen 1997a did not report on the presence of nausea and vomiting.

Figure 5. Forest plot of comparison: 2 Ibuprofen vs placebo in Children, outcome: 2.1 Pain-free.



The quality of evidence for the pain-free outcome was low, downgraded by two levels due to very serious imprecision (Summary of findings 1).

Ibuprofen versus placebo in adolescents

One small three-way cross-over study examined ibuprofen, zolmitriptan, and placebo (Evers 2006). While it included both children and adolescents, the mean participant age was 13.9 years (N = 29), so we considered the study to be predominantly in adolescents. Headache relief at two hours was the primary outcome measure reported, but investigators also reported pain freedom at two hours. The pain-free outcome was not statistically significant (RR 7.00, 95% CI 0.99 to 49.69), but ibuprofen was statistically superior to placebo for headache relief (RR 2.50, 95% CI 1.02 to 6.10). There were no significant differences in other secondary outcome measures, including use of rescue medication, headache recurrence, presence of nausea, or presence of vomiting. There was no significant difference in adverse events observed.

Triptans versus placebo in children

Three studies examined two triptan medications in children under 12 years of age: rizatriptan (Ho 2012, N = 200) and sumatriptan (Hämäläinen 2002, N = 59; Ueberall 1999, N = 14). Triptans as a class of medication were superior to placebo in children for the primary outcome measure of pain freedom (RR 1.67, 95% CI 1.06 to 2.62; Analysis 2.1) with a NNTB of 13. There were no statistically significant differences in the effect size between rizatriptan and sumatriptan subgroups. Overall, we did not observe any statistically significant difference in the secondary outcomes of headache relief (Analysis 2.3), rescue medication (Analysis 2.4), headache recurrence (Analysis 2.5), presence of nausea (Analysis 2.6), or presence of vomiting (Analysis 2.7). There was no statistically significant difference in the proportion of adverse events observed in the triptan versus placebo groups (Analysis 2.2).

The quality of evidence for the pain-free outcome was moderate, downgraded by one level due to serious imprecision (Summary of findings 2).

Triptans versus placebo in adolescents

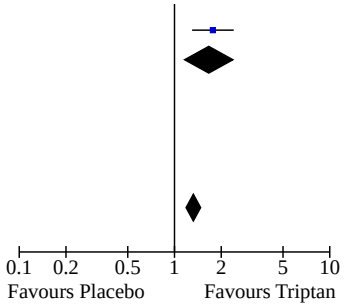
Triptans as a class of medications were superior to placebo in adolescents for the acute treatment of migraine (Figure 6). Overall the pain-free RR was 1.32 (95% CI 1.19 to 1.47; Analysis 3.1) with a NNTB of 6 and low (I^2 = 26%), non-significant heterogeneity (P = 0.13) between studies. Triptans for which there were two or more studies were statistically superior to placebo as a subgroup (Figure 6), but subgroup differences in effect size were not statistically significant. The individual triptans included were almotriptan (Linder 2008, N = 714), eletriptan (Winner 2007, N = 274), naratriptan (Rothner 1997, N = 300), rizatriptan (Ahonen 2006, N = 96; Winner 2002, N = 296; Ho 2012, N = 570; Visser 2004a, N = 476), sumatriptan (Ahonen 2004, N = 83; Callenbach 2007, N = 46; Fujita 2014, N = 144; Hämäläinen 1997b, N = 23; Rothner 1999a, N = 273; Rothner 1999b, N = 92; Rothner 1999c, N = 102; Winner 1997, N = 298; Winner 2000, N = 507; Winner 2006, N = 731), and zolmitriptan (Evers 2006, N = 29; Lewis 2007, N = 171; NCT01211145, N = 584; Rothner 2006, N = 696). There was, however, an increased risk of minor (non-serious) adverse events in the triptan group when compared with placebo, with an RD of 0.13 (95% CI 0.08 to 0.18; Analysis 3.2) and NNTH of 8. The secondary efficacy outcomes that favoured triptans were headache relief (RR 1.14, 95% CI 1.04 to 1.24; Analysis 3.3), a reduction in the use of rescue medication (RR 0.79, 95% CI 0.72 to 0.87; Analysis 3.4), and reduced risk of headache recurrence (RR 0.79, 95% CI 0.68 to 0.93; Analysis 3.5). There were no statistically significant differences in the presence of nausea (Analysis 3.6) or vomiting (Analysis 3.7).

Figure 6. Forest plot of comparison: 7 Triptans vs placebo in Adolescents, outcome: 7.1 Pain-free.

Study or Subgroup	Triptan Events	Triptan Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 Almotriptan						
Linder 2008	212	544	60	170	10.6%	1.10 [0.88 , 1.39]
Subtotal (95% CI)		**544**		**170**	**10.6%**	**1.10 [0.88 , 1.39]**
Total events:	212		60			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.85 (P = 0.40)						
3.1.2 Eletriptan						
Winner 2007	31	141	20	133	3.6%	1.46 [0.88 , 2.43]
Subtotal (95% CI)		**141**		**133**	**3.6%**	**1.46 [0.88 , 2.43]**
Total events:	31		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.46 (P = 0.14)						
3.1.3 Naratriptan						
Rothner 1997	52	226	16	74	3.8%	1.06 [0.65 , 1.75]
Subtotal (95% CI)		**226**		**74**	**3.8%**	**1.06 [0.65 , 1.75]**
Total events:	52		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.25 (P = 0.81)						
3.1.4 Rizatriptan						
Ahonen 2006	34	96	17	96	3.7%	2.00 [1.20 , 3.33]
Winner 2002	48	149	40	142	6.4%	1.14 [0.81 , 1.62]
Ho 2012	87	284	62	286	8.5%	1.41 [1.07 , 1.87]
Visser 2004a	91	233	75	240	9.8%	1.25 [0.98 , 1.60]
Subtotal (95% CI)		**762**		**764**	**28.4%**	**1.34 [1.13 , 1.60]**
Total events:	260		194			
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 3.61$, df = 3 (P = 0.31); $I^2 = 17\%$						
Test for overall effect: Z = 3.28 (P = 0.001)						
3.1.5 Sumatriptan						
Hämäläinen 1997b	5	23	2	23	0.5%	2.50 [0.54 , 11.60]
Rothner 1999b	9	62	3	30	0.7%	1.45 [0.42 , 4.98]
Rothner 1999c	11	66	5	36	1.1%	1.20 [0.45 , 3.18]
Callenbach 2007	12	46	9	46	1.8%	1.33 [0.62 , 2.86]
Rothner 1999a	43	208	10	35	2.9%	0.72 [0.40 , 1.30]
Fujita 2014	16	74	20	70	3.0%	0.76 [0.43 , 1.34]
Ahonen 2004	26	83	17	83	3.4%	1.53 [0.90 , 2.60]
Winner 1997	58	222	14	76	3.5%	1.42 [0.84 , 2.39]
Winner 2000	116	377	32	130	6.8%	1.25 [0.89 , 1.75]
Winner 2006	191	483	68	242	10.5%	1.41 [1.12 , 1.77]
Subtotal (95% CI)		**1644**		**771**	**34.3%**	**1.27 [1.10 , 1.48]**
Total events:	487		180			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 8.94$, df = 9 (P = 0.44); $I^2 = 0\%$						
Test for overall effect: Z = 3.15 (P = 0.002)						
3.1.6 Zolmitriptan						
Evers 2006	6	14	1	14	0.3%	6.00 [0.83 , 43.59]
Lewis 2007	58	148	24	127	5.1%	2.07 [1.37 , 3.13]
Rothner 2006	108	483	32	162	6.4%	1.13 [0.80 , 1.61]
NCT01211145	86	288	50	296	7.6%	1.77 [1.30 , 2.41]
Subtotal (95% CI)		**933**		**599**	**19.3%**	**1.66 [1.16 , 2.38]**

Figure 6. (Continued)

NCT01211145	86	288	50	296	7.6%	1.77 [1.30 , 2.41]
Subtotal (95% CI)		**933**		**599**	**19.3%**	**1.66 [1.16 , 2.38]**
Total events:	258		107			
Heterogeneity: Tau² = 0.07; Chi² = 7.34, df = 3 (P = 0.06); I² = 59%						
Test for overall effect: Z = 2.79 (P = 0.005)						
Total (95% CI)		**4250**		**2511**	**100.0%**	**1.32 [1.19 , 1.47]**
Total events:	1300		577			
Heterogeneity: Tau² = 0.01; Chi² = 27.11, df = 20 (P = 0.13); I² = 26%						
Test for overall effect: Z = 5.11 (P < 0.00001)						
Test for subgroup differences: Chi² = 4.72, df = 5 (P = 0.45), I² = 0%						



The quality of evidence for the pain-free outcome was moderate, downgraded by one level due to serious inconsistency (Summary of findings 3).

Sumatriptan plus naproxen sodium versus placebo in adolescents

We included one study of sumatriptan plus naproxen sodium versus placebo. The study included adolescents with a mean age of 14.7 years and randomized a total of 683 participants. The doses of sumatriptan + naproxen sodium, respectively, were 10 mg + 60 mg (N = 96), 30 mg + 180 mg (N = 97), and 85 mg + 500 mg (N = 152). The primary outcome reported was pain freedom at two hours, with data adjusted for age and baseline severity. The adjusted pain-free rates at two hours were higher with sumatriptan + naproxen sodium 10 mg + 60 mg (29%; adjusted P = 0.003), 30 mg + 180 mg (27%; adjusted P = 0.003), and 85 mg + 500 mg (24%; adjusted P = 0.003) versus placebo (10%). Post hoc analyses showed no differences among the 3 doses or an age-by-treatment interaction. Calculating the RR for pain relief at 2 hours, sumatriptan + naproxen sodium was superior to placebo with an RR of 3.25 (95% CI 1.78 to 5.94) and NNTB of 6. The use of rescue medication was also significantly reduced with the combination medication when compared with placebo (RR 0.46, 95% CI 0.32 to 0.64), but investigators did not report headache relief. There was no statistically significant increase in adverse events and no difference in the presence of nausea. Headache recurrence and presence of vomiting were also not reported.

The quality of evidence for the pain-free outcome was moderate, downgraded by one level due to the width of the confidence interval of the effect size (Summary of findings 4).

Dihydroergotamine (DHE) versus placebo in children

One small cross-over study of dihydroergotamine versus placebo included children and adolescents aged 5 to 15 years (Hämäläinen 1997c, N = 13). With a mean participant age of 10.3 years, we considered the study to be predominantly in children. DHE demonstrated no significant difference in the pain-free outcome or any of the secondary outcomes, including headache relief or the use of rescue medications. There was no statistically significant increase in the proportion of adverse events between DHE and placebo. Authors did not report headache recurrence, presence of nausea, or the presence of vomiting.

Subgroup analysis for other sources of heterogeneity

We assessed potentially important sources of clinical heterogeneity using the pain-free outcome of triptan studies in adolescents. Tests for subgroup differences showed that effect size estimates for intranasal studies of sumatriptan and zolmitriptan were significantly higher than oral triptan studies of almotriptan, eletriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan (P = 0.02, I^2 = 81.5%, Analysis 4.1). We observed a statistically significant difference in the comparison of oral versus intranasal zolmitriptan studies, where intranasal delivery was associated with a significantly higher effect size for the pain-free outcome (P = 0.04)=, I^2 = 77.1%; Analysis 4.3). However, the difference was not statistically significant when comparing oral versus intranasal sumatriptan studies (Analysis 4.2). The permitted concomitant use of migraine preventive medications in the triptan trials among adolescents was not associated with any significant difference in the effect size (Analysis 4.4). We did not observe any statistically significant differences in the overall effect size estimates between the triptan versus placebo studies that included only children, those where children and adolescents were mixed and not reported separately, and those studies that examined adolescents exclusively (P = 0.42, I^2 = 0%; Analysis 5.1).

Sensitivity analysis of other study characteristics

The overall heterogeneity was low for the triptan versus placebo studies in adolescents for the pain-free outcome (Tau^2 = 0.01; Chi^2 = 27.15, degrees of freedom (df) = 20 (P = 0.13); I^2 = 26%). We performed a sensitivity analysis to explore the effects of sponsorship; risk of bias in allocation concealment; study design (cross-over versus parallel group); type of study report (journal article versus clinical trial registry and abstract); and small sample size (< 50). The cross-over study design was associated with significantly higher effect size estimates for the pain-free outcome (P = 0.004, I^2 = 88.2%; Analysis 6.1). The effect estimate for the triptan versus placebo studies in adolescents was similar in direction, magnitude, and significance (i.e. RR 1.25, 95% CI 1.12 to 1.39) when we removed studies of cross-over design. Similarly studies with a sample size of less than 50 had a significantly higher estimates of treatment effect (P = 0.03, I^2 = 79.4%; Analysis 6.5). The overall effect estimate without studies having small sample sizes was similar to the reported effect estimate (RR 1.31, 95% CI 1.18 to 1.46). There were no significant subgroup difference for allocation concealment (Analysis 6.2), source of funding (Analysis 6.3), or type of study report (Analysis 6.4).

DISCUSSION

Summary of main results

In total, we identified 27 moderate quality studies for inclusion. Most were at a low or unclear risk of bias and of varying size (a range of 13 to 888 participants in total). The mean age of inclusion was 12.9 years with a range of means between 8.2 and 14.7 years.

Paracetamol

There is insufficient evidence in favor of paracetamol for the acute treatment of migraine in children or adolescents. We only identified one small cross-over study, predominantly in children, where oral paracetamol was not superior to placebo or ibuprofen.

Ibuprofen

Ibuprofen was more effective than placebo in producing pain freedom in two small studies involving children. In one small cross-over study in adolescents, ibuprofen was not superior to placebo for pain freedom, but it was for headache relief (Evers 2006). While ibuprofen as a non-steroidal anti-inflammatory drug (NSAID) may have some advantage in the treatment of a migraine attack, considering the presence of neurogenic inflammation (Levy 2008), it was not superior to zolmitriptan or paracetamol in two three-way cross-over studies (Evers 2006; Hämäläinen 1997a). Ibuprofen was not associated with an increase in adverse events overall.

Triptans

Triptans as a class of medication were more effective than placebo in producing pain freedom in 3 studies involving children and 21 studies involving adolescents. We did not observe any significant differences in the effect sizes between the subgroups of individual triptans, including almotriptan, eletriptan, naratriptan, rizatriptan, sumatriptan, or zolmitriptan. While there was some evidence to suggest that intranasal preparations of sumatriptan and zolmitriptan produce higher effect sizes than oral preparations of all the triptans listed above, the evidence was inconsistent. Evidence for the efficacy of the triptans was variable, as measured through the secondary outcomes of headache relief, use of rescue medication, headache recurrence, presence of nausea, and presence of vomiting, but in general it favored the triptans. The efficacy, however, is counterbalanced with an increased risk of minor (non-serious) adverse events overall. However, there were no serious adverse events reported. Commonly reported adverse events included fatigue, dizziness, asthenia, dry mouth, and nausea or vomiting with oral preparations, and taste disturbance, nasal symptoms, and nausea with intranasal preparations. The combination of sumatriptan with naproxen sodium was also more effective than placebo in producing pain freedom in one adolescent study. We did not observe any significant differences in the effect sizes between studies that included children versus adolescents. The only significant study characteristic that was associated with a higher effect size was the use of a cross-over design versus parallel group design.

Dihydroergotamine

There is insufficient evidence for oral dihydroergotamine in the treatment of migraine in children or adolescents. We only identified one small cross-over study, which found that oral dihydroergotamine was not superior to placebo.

Overall completeness and applicability of evidence

Of the 27 randomized controlled trials we identified on migraine symptom relieving medications used in the outpatient setting for children and adolescents, 24 belonged to the triptan class, including almotriptan, eletriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan. Pharmaceutical companies sponsored most of the triptan studies (N = 19). We only identified three studies of the most frequently used pain medications (paracetamol and ibuprofen) and none examining other non-steroidal anti-inflammatory drugs (NSAIDs) or early treatment (Goadsby 2008; Suthisisang 2010). We only identified one study on a combination medication (sumatriptan plus naproxen sodium).

Quality of the evidence

We judged the quality of evidence for the effect of triptans on pain relief to be moderate, having downgraded it due to serious inconsistency in adolescents and imprecision in children (small sample size, few events, and wide confidence intervals. For ibuprofen, we downgraded the quality of the evidence by two levels to low due to very serious imprecision (small sample size, few events, and wide confidence intervals). It is likely that future research will help to tighten the confidence intervals around the effect size of the above medications. More evidence is needed to assess the effect of paracetamol in children and adolescents. Although we identified heterogeneity between the results in the triptan studies, we believe that further research is unlikely to change the direction of the effect.

Potential biases in the review process

The reviewers searched the indexed and gray literature extensively to identify all published and unpublished studies of medications used in the treatment of migraine in children and adolescents. Pharmaceutical company clinical trial registries were available for sumatriptan, sumatriptan + naproxen sodium, rizatriptan, and zolmitriptan studies, and we identified some negative trials in these sources. The absence of trial registries for the other medications may bias the identification of other negative trials. The funnel plot examination suggested some potential for publication bias, but the Egger statistical tests for bias were not significant.

Agreements and disagreements with other studies or reviews

A number of similar systematic reviews have been published. The review by Major 2003 of triptan studies in children and adolescents aged 6 to 18 years concluded that intranasal sumatriptan was effective, while other oral triptans were not. The American Academy of Neurology Quality Standards Subcommittee and the Practice Committee of the Child Neurology Society have published a practice parameter on the pharmacological treatment of migraine (Lewis 2004). Our conclusions are similar with regard to the evidence for efficacy of ibuprofen in children but differ with regard to the efficacy of paracetamol. The practice parameter also concluded that sumatriptan nasal spray was effective for the acute treatment of migraine in adolescents. Damen 2005 evaluated all randomized controlled trials for the acute treatment of migraine in children and adolescents less than 18 years of age but identified a smaller number of trials (10 studies). The authors performed a meta-analysis, and concluded there was evidence for the use of ibuprofen, paracetamol, and intranasal sumatriptan. Silver 2008 also included all medications for the acute treatment of migraine

in their search, but identified only 11 studies in children and adolescents under 18 years of age. The authors concluded that there was evidence only for the use of ibuprofen and sumatriptan and did not differentiate between oral and intranasal sumatriptan preparations. A meta-analysis and qualitative review of ibuprofen and paracetamol in adults, adolescents, and children concluded that ibuprofen was at least as efficacious as paracetamol (Pierce 2010). Eiland 2010 recommended the triptan class as an acute treatment option for children and adolescents with migraines, also concluding that there was evidence to recommend sumatriptan and zolmitriptan nasal sprays as well as rizatriptan or almotriptan tablets over the other triptans. Vollono 2011 examined 11 studies and concluded that triptans are an important option in the symptomatic treatment of childhood and adolescent migraine. Individually, they found that zolmitriptan and rizatriptan were superior to placebo in most studies, and almotriptan was well tolerated. Toldo 2012 recommended paracetamol and ibuprofen as first line treatments for migraine in children and adolescents. The triptans were deemed safe, and the authors concluded that sumatriptan nasal spray was more effective than placebo and that zolmitriptan nasal spray and rizatriptan tablets were likely effective. Wöber-Bingöl 2013 examined 14 studies on triptans in adolescents and 6 studies in children and concluded that evidence for the acute pharmacological treatment of migraine in children was poor, but evidence for adolescents was better, albeit still limited. The authors outlined that sumatriptan nasal spray and zolmitriptan nasal spray were approved for adolescents in Europe; while in the United States almotriptan can be used for adolescents and rizatriptan is approved for patients aged 6 to 17 years. The combination of sumatriptan and naproxen sodium in adolescents has also since been approved for use in adolescents in the United States. Bonfert 2013 included 33 studies examining acute and preventive treatment for migraine and tension-type headaches. The reviewers did not conduct a meta-analysis but reviewed the individual studies, concluding that ibuprofen and paracetamol should be considered first and second line therapies for the acute treatment of migraine in children and adolescents, with almotriptan and rizatriptan as suitable third-line agents.

Finally, a recent review identified only seven studies in adolescents aged 12 to 17 years and concluded that enrichment designs significantly reduced placebo response (Sun 2013). Our review includes a higher number of studies (N = 27), including negative studies published only in pharmaceutical-industry sponsored trial registries. We draw similar conclusions with regard to the benefit and safety of ibuprofen in treating children and adolescents with migraine. As with previous reviews, the low cost, broad availability, and safety may make ibuprofen a preferred first choice. We differ however in our conclusion that there is insufficient evidence to recommend paracetamol. In general our conclusions are similar with regard to the triptans as a class of medication being effective in the treatment of children and adolescents with migraine. We differ in that we found insufficient evidence to recommend one triptan over the others in our meta-analysis and sub-group analyses. While rizatriptan, sumatriptan, and zolmitriptan were statistically superior to placebo as subgroups, the overall test for subgroup heterogeneity was not significant. In our meta-analysis, we combined the studies of triptan medications irrespective of route of delivery and dosage.

AUTHORS' CONCLUSIONS

Implications for practice

We found low quality evidence from two small studies that ibuprofen appears to improve pain relief in children with migraine. We have only limited information on adverse events in the trials included in this review. There is insufficient evidence in favor of paracetamol. We did not identify evidence regarding early treatment, the use of other NSAIDs, or the combination of these analgesics with other medications (e.g. metoclopramide, caffeine) in children or adolescents.

For children and adolescents with migraine, triptans appear to be effective in the acute treatment of migraine. Sumatriptan plus naproxen sodium is effective in adolescents, but we did not find any studies in children. Triptans are generally safe but carry an increased risk of minor (non-serious) adverse events.

For clinicians, the choice of triptan medication may be guided by factors such as patient preference, route of delivery, or palatability. A parent who responds well to one of the medications may be more likely to request that medication for their child. More than half of the triptan studies in children and adolescents were of sumatriptan, and this medication serves as the reference drug in this class. The choice of triptan may also be based on local availability, drug cost reimbursement, and regulatory approval. We found inconsistent evidence in our subgroup analysis of the intranasal versus oral triptan preparations, but patients may prefer one route over the other (e.g. intranasal if significant vomiting or oral if patient has chronic rhinitis).

For policymakers and funders, the triptan class of medications, as well as sumatriptan in combination with naproxen sodium, are suitable options for children and adolescents with migraine. One or more of these medications should be made available in situations where ibuprofen has failed to provide pain freedom or headache relief.

Implications for research

General

Future studies should separate the childhood and adolescent age groups to enable separate meta-analyses of these groups. More studies of simple analgesics commonly used in the treatment of migraine like paracetamol and ibuprofen, other NSAIDs, or head to head comparisons are warranted.

Design

Studies employing a cross-over design were associated with significantly higher effect size estimates. Similar findings have been reported previously (Lathyris 2007). This may have been due to inadequate blinding in cross-over studies or higher effect estimates due to the smaller sample size. Guidelines for controlled trials of drugs in migraine advocate the use of either cross-over or parallel design (Tfelt-Hansen 2012).

Measurement (endpoints)

Pain freedom as an outcome measure demonstrated low heterogeneity between studies and may be most suitable as a primary outcome measure. Data on other outcome measures (e.g. nausea, headache relief, etc.) should also be collected, as described

in the guidelines for controlled trials of drugs in migraine (Tfelt-Hansen 2012).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ahonen 2004

Study characteristics	
Methods	Randomized, double-blind, placebo-controlled, two-way cross-over trial of sumatriptan nasal spray
Participants	Children and adolescents 8-17 years and body weight ≥ 20 kg with a diagnosis of migraine with or without aura meeting the IHS 1988 criteria from 3 pediatric hospitals in Finland. Participants were expected to have least 2 migraine attacks per month lasting 4 h and demonstrated resistance to usual therapy for migraine with paracetamol or nonsteroidal anti-inflammatory drugs (NSAIDs). No participants were receiving preventive medication. Randomized (N = 129); medication not used (N = 35); 1 medication used (N = 11); intention-to-treat analysis (N = 94); primary efficacy analysis (N = 83)
Interventions	Sumatriptan nasal spray 10 mg (weight 20 to 39 kg) or 20 mg (≥ 40 kg) versus placebo. Children were instructed to take a single nasal insufflation at the onset of a migraine attack if headache severity was classified as ≥ 3 on a 5-faces pain intensity scale. Each participant treated 2 migraine attacks - 1 with placebo and the other with sumatriptan. Rescue medications were allowed at any point.
Outcomes	• Headache relief at 2 h (defined as severe or moderate (a grade of ≥ 3) to at least 2 grades lower or fell asleep during these 2 h and was pain-free on awakening) • Pain-free at 2 h • Use of rescue medication • Adverse events Other reported outcomes: • Headache relief and pain-free at 1, 3, and 4 h after treatment • Participant preference
Headache severity scale	5-faces pain scale (5 severe, 4 to 3 moderate, 2 mild, 1 no pain)
Funding source	GlaxoSmithKline
Publication	Journal
Notes	All children who had used at least 1 treatment were included in the intention-to-treat analysis

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was done in the hospital pharmacy"

Ahonen 2004 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "The randomization code was stored by one of the authors who did not meet any of the patients, and it was not broken until the database of treatment efficacy was created and locked"
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "study drugs of identical appearance"; "indistinguishable". Comment: Probably done, since both preparations were supplied by GlaxoSmithKline
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: study drug and placebo groups were balanced
Selective reporting (reporting bias)	Low risk	Comment: all primary outcomes were reported

Ahonen 2006

Study characteristics	
Methods	Randomized, placebo-controlled, double-blind, 3-way cross-over trial of oral rizatriptan
Participants	Children or adolescents between 6 and 17 years of age, body weight ≥ 20 kg, headache meeting the IHS 1988 criteria for migraine with or without aura from the 2 pediatric hospitals in Finland. Participants were expected to have at least 2 migraine attacks per month lasting 4 h or more and previous unsatisfactory with paracetamol or NSAIDs. None of the children were receiving preventive therapy. Randomized (N = 147); medication not used (N = 31); 1 medication used (N = 10); 2 treatments used (N = 10); intention-to-treat analysis (N = 116); primary efficacy analysis (N = 96)
Interventions	Rizatriptan 5 mg (weight 20 to 39 kg) or rizatriptan 10 mg (weight ≥ 40 kg) and placebo. Each participant treated 3 migraine attacks (2 with rizatriptan and 1 with placebo) at the onset of the attack if headache severity was ≥ 3 on the 5-point scale. Rescue medications were allowed at any time, but encouraged to be taken only after 2 h.
Outcomes	• Headache relief at 2 h (defined as severe or moderate (a grade of ≥ 3) to at least 2 grades lower or fell asleep during these 2 h and was pain-free on awakening) • Pain-free at 2h • Adverse events • Use of rescue medication Other reported outcomes: • Headache relief and pain-free at 1, 3, and 4 h after treatment • Participant preference
Headache severity scale	5-faces pain scale (5 severe, 4 to 3 moderate, 2 mild, 1 no pain)
Funding source	Not specified
Publication	Journal
Notes	All children who had used at least 1 treatment were included in the intention-to-treat analysis
Risk of bias	

Ahonen 2006 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "tossing a coin method"
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was done in the hospital pharmacy"; "randomization code was stored by one of the authors. . . was not broken until the database of treatment efficacy was created and locked"
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "drugs packed in capsules of identical appearance"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: missing outcome data balanced across intervention groups
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported

Callenbach 2007

Study characteristics	
Methods	Randomized, double-blind, placebo-controlled, cross-over, 2-attack study of sumatriptan nasal spray
Participants	Participants from 18 centres in the Netherlands were 12-17 years of age with a diagnosis of migraine with or without aura per revised IHS 1988 criteria (Winner 1995) whom had failed, or responded inadequately, to at least 1 over the counter or prescription medication for migraine, duration typically longer than 4 hours if untreated, and between 1 and 8 attacks per month in each of the 2 months before enrolment Randomized (N = 66); withdrawn (N = 20); analyzed (N = 46)
Interventions	Each participant treated 2 attacks - 1 with sumatriptan nasal spray (10 mg if < 40 kg or 20 mg if > 40 kg) and 1 with placebo nasal spray. Recurrence within 2-24 h could be treated with a second dose.
Outcomes	• Headache relief at 2 h • Pain free at 2 h • Presence of nausea, • Use of rescue medication • Adverse events • Recurrence of migraine within 2-2h h Other reported outcomes: • Headache relief, pain free, nausea, vomiting, photophobia, and phonophobia at 15, 30, and 60 min
Headache severity scale	4-point scale (none, mild, moderate, severe)
Funding source	GlaxoSmithKline
Publication	Journal and Clinical Trial Registry
Notes	—

Callenbach 2007 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "in a randomized order" Comment: other studies funded by GlaxoSmithKline reported acceptable sequence generation (e.g. Winner 2007)
Allocation concealment (selection bias)	Unclear risk	Comment: no information provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Comment: no information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: withdrawals balanced across intervention groups
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported

Derosier 2012

Study characteristics	
Methods	Outpatient, double-blind, randomized, placebo-controlled, parallel group trial with an enrichment design of oral sumatriptan + naproxen sodium
Participants	Eligible participants were 12 to 17 years old at screening and had > 6 months history of 2 to 8 migraine attacks per month (with or without aura: ICHD-2), typically lasting > 3 h and associated with moderate to severe headache pain. Triptan-naïve subjects were eligible. Run-in phase (N = 976); Randomized (N = 589); Medication not used (N = 57); Withdrawn (N = 42); intention-to-treat and primary efficacy analysis (N = 490)
Interventions	Subjects treating 1 moderate to severe migraine with single-blind placebo during the run-in phase and reporting pain 2 h post dose (placebo non responders) were randomly assigned into the double-blind phase. In the double-blind phase, subjects treated 1 moderate to severe migraine with either matching placebo or sumatriptan + naproxen sodium 10 mg + 60 mg, 30 mg + 180 mg, or 85 mg + 500 mg.
Outcomes	• Pain-free at 2 h post-treatment in the double-blind phase (absence of headache pain post-treatment from moderate or severe at baseline, without previous use of rescue medication) • Nausea free at 2 h • Use of rescue medication within 2-24 h Other reported outcomes: • Sustained freedom from pain, photophobia, phonophobia, and nausea from 2-24 h post-treatment
Headache severity scale	4-level pain scale (none, mild, moderate, severe)
Funding source	GlaxoSmithKline
Publication	Journal and Clinical Trial Registry

Derosier 2012 *(Continued)*

Notes	Single-blind run-in phase (enrichment design) assessment was at 2 h

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Upon determination of subject eligibility and completion of the randomizations visit, site staff telephoned an interactive voice response system and dispensed randomly assigned, age-group stratified treatment."
Allocation concealment (selection bias)	Low risk	Comment: used interactive voice response system for randomization
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Parent/guardian and subject were informed that they would not know which study drug was provided for the first or second migraine treated, and that the investigator would not know which study drug was provided for the second migraine treated. To maintain blinding, sites received education on describing the single-blind phase.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: withdrawals and reasons for withdrawal (outlined in Figure 1 of Derosier 2012) were balanced between groups
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes were reported

Evers 2006

Study characteristics

Methods	Double-blind, placebo-controlled, cross-over study to investigate the efficacy of oral zolmitriptan in the treatment of migraine attacks in children and adolescents
Participants	Children and adolescents aged 6-18 years from an headache outpatient clinic (not reported separately) Migraine with and without aura according to the criteria of the ICHD-2 No neurologic, psychiatric, and vascular disorder Randomized (N = 32); withdrawn (N = 3); intention-to-treat and primary efficacy analysis (N = 29)
Interventions	Ibuprofen 200 mg PO (children under 12) or 400 mg PO (adolescents) Zolmitriptan 2.5 mg PO
Outcomes	• Pain relief (defined as no or mild headache after moderate or severe headache) after 2 h • Pain free after 2 h • Headache recurrence and use of rescue medication within 24 h • Nausea and vomiting after 2 h • All adverse events classified (probably/possibly drug related or not drug related) Other reported outcomes: • Pain-free and headache relief after 0.5, 1, 4, and 24 h • Headache recurrence, sustained pain-free response, frequency of accompanying symptoms (nausea, vomiting, photophobia, phonophobia) after 0.5, 1, 3, and 24 h

Evers 2006 *(Continued)*

Headache severity scale	4-point scale (none, mild, moderate, severe)
Funding source	Not clear
Publication	Journal
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The order of the study drugs was randomized for every patient."
Allocation concealment (selection bias)	Low risk	Comment: cross-over study where each participant received the study drugs in random order
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Comment: blinding was not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 3 of 32 participants dropped out (withdrawal of consent N = 2) lost to follow-up N = 1)
Selective reporting (reporting bias)	Low risk	Comment: aAll primary and secondary outcomes were reported

Fujita 2014

Study characteristics

Methods	Randomized, double-blind, placebo-controlled, parallel group trial of oral sumatriptan
Participants	Participants from 17 centres in Japan were 10-17 years of age, diagnosed with migraine with or without aura per ICHD-2 criteria for a minimum of 6 months, and 2-8 attacks monthly lasting for > 3 h in the last 2 months prior to entry. Randomized (N = 178); withdrawn (N = 34); intention-to-treat and primary efficacy analysis (N = 144)
Interventions	Oral sumatriptan 25 mg (1 tablet and 1 matching placebo), sumatriptan 50 mg (2 tablets), or placebo (2 tablets) taken as soon as possible (within 30 minutes) after the development of a migraine with grade 3 or more pain
Outcomes	• Headache relief (reduction of 2 grades) at 2 h • Pain-free at 2 h • Presence of nausea, vomiting at 2 h • Use of rescue medications from time of dosing to 4 h post-treatment • Adverse events Other reported outcomes: • Headache relief, pain-free, photophobia, phonophobia, and vomiting at 0.5, 1, and 4 hours post-treatment

Fujita 2014 *(Continued)*

Headache severity scale	5-grade scale
Funding source	GlaxoSmithKline
Publication	Journal and Clinical Trial Registry
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Investigator (or subinvestigator) completed the registration form and sent it to the randomization center by facsimile. The randomization center. . . assigned a randomization number to the patient."
Allocation concealment (selection bias)	Low risk	Quote: "For allocation of the participants, a computer-generated list of random numbers was used."
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "The investigator (or subinvestigator) dispensed the investigational product to the patient according to the computer-generated randomization number."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: used last observation carried forward (LOCF)
Selective reporting (reporting bias)	Low risk	Comment: all stated outcomes were reported

Ho 2012

Study characteristics

Methods	Randomized, double-blind, placebo-controlled, parallel group trial of oral rizatriptan with an enrichment design
Participants	Participants were males and females aged 6–17 years who were ≥ 20kg in weight and who had at least a 6-month history of migraine attacks with or without aura as defined by ICHD-2, usually lasting 3 h or more (when untreated). Participants had ≥ 1 and ≤ 8 moderate to severe migraine attacks with or without aura per month in the 2 months before the screening visit, and had not, by history, experienced satisfactory relief with NSAIDs or paracetamol. Patients were excluded if they had not experienced satisfactory relief from migraine pain during prior treatment with 2 or more adequate courses of triptans. Non-responders to placebo in stage 1 were randomized 1:1 to rizatriptan:placebo, with randomization stratified by age (6–11 years versus 12–17 years). Randomized (N = 1382); not treated (N = 405); randomized in stage 1 (N = 915); randomized in stage 2 (N = 791); withdrawn (N = 21); intention-to-treat and primary efficacy analysis (N = 770)
Interventions	Oral-disintegrating tablet of rizatriptan 5 mg (< 40 kg) or 10 mg (≥ 40 kg) or placebo. Participants treated within 30 min of a moderate/severe migraine attack. In stage 1, participants were randomized 20:1 to placebo or rizatriptan. In stage 2, participants with ongoing moderate/severe pain after 15 min (non-responders) who received placebo in stage 1 were randomized 1:1 to rizatriptan or placebo.
Outcomes	• Pain-free at 2 h • Pain relief (reduction of at least 2 grades from baseline) at 2 h

Ho 2012 *(Continued)*

	• Vomiting, nausea free at 2 h • Use of rescue medications within 24 h • Adverse events Other reported outcomes: • Sustained pain-free 24 and 48 h post-treatment • Photophobia-free, phonophobia-free at 2 h
Headache severity scale	4-point scale (none, mild, moderate, severe)
Funding source	Merck
Publication	Journal and abstract
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: randomization process not described
Allocation concealment (selection bias)	Unclear risk	Comment: allocation performed using interactive voice response system
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Comment: no information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: withdrawals are balanced between intervention groups
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported including adverse events

Hämäläinen 1997a

Study characteristics	
Methods	Randomized, double-blind, placebo-controlled, 3-way cross-over trial of ibuprofen, paracetamol, and placebo
Participants	Children or adolescents < 18 years with a diagnosis of migraine with or without aura meeting IHS 1988 criteria from 3 pediatric hospitals in the Greater Helsinki Area of Finland who found previous therapy for migraine unsatisfactory. Participants were required to have 2 migraine attacks per month lasting 2 h or more. Randomized (N = 106); lost to follow-up (N = 2); medication not used (N = 16); 1 medication used (N = 5); 2 medications used (N = 8); withdrawn (N = 9); intention-to-treat analysis (N = 88); primary efficacy analysis (N = 66)
Interventions	Each participant treated 1 of 3 migraine attacks with either oral paracetamol (15 mg/kg), oral ibuprofen (10 mg/kg), or placebo. The active drugs and matching placebo were supplied by the University

Hämäläinen 1997a *(Continued)*

	Pharmacy of Helsinki in 3 mixtures containing peppermint water, black currant syrup, sugar syrup, and either 30 mg/ml paracetamol or 20 mg/ml ibuprofen, or, as a placebo, cellulose. Each participant received a package of 3 identically numbered bottles and a plastic 10 ml syringe for exact weight-based dosing (0.5 ml/kg, maximum dose 30 ml).
Outcomes	• Headache relief at 2 h (defined as severe or moderate (a grade of ≥ 3) to at least 2 grades lower • Pain-free at 2 h • Use of rescue medication within 2 h • Adverse events Other reported outcomes: • Headache relief and pain-free at 1 h after treatment • Patient preference
Headache severity scale	Participants were allowed to choose between the 5-faces pain scale (5 severe, 4 to 3 moderate, 2 mild, 1 no pain) or the 100 mm visual analogue scale (VAS). The VAS (0 to 100) data were transformed to a nominal scale: grade 1: 0 to ≤ 12; grade 2: 12 to ≤ 37; grade 3: 37 to ≤ 62; grade 4: 62 to ≤ 87; and grade 5: 87 to ≤ 100
Funding source	Not specified
Publication	Journal
Notes	All additional children and adolescents with any data on efficacy were included in the intention-to-treat analysis, which was performed without regard to pain intensity at the start of the attack.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: no information provided
Allocation concealment (selection bias)	Unclear risk	Comment: no information provided
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "[T]he active drugs and matching placebo were supplied by the University Pharmacy of Helsinki in three mixtures containing peppermint water, black currant syrup, sugar syrup, and either 30 mg/ml paracetamol or 20 mg/ml ibuprofen, or as placebo (cellulose). Each participant received a package of three identically numbered bottles and a plastic 10 ml syringe for exact weight-based dosing (0.5 ml/kg; max 30 ml)."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: missing outcome data balanced across intervention groups
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported

Hämäläinen 1997b

Study characteristics	
Methods	Randomized, double-blind, placebo-controlled, 2-way cross-over trial of oral sumatriptan

Hämäläinen 1997b *(Continued)*

Participants	Children or adolescents 8-17 years with a diagnosis of migraine with or without aura meeting IHS 1988 criteria from 3 pediatric hospitals in the Greater Helsinki Area of Finland who had not benefited from previous migraine therapy. Participants were required to have 2 migraine attacks per month. None of the participants were using preventive therapy, but had already participated in previous placebo-controlled trials with paracetamol and ibuprofen, dihydroergotamine, or both. Randomized (N = 31); medication not used (N = 4); 1 medication used (N = 3); withdrawn (N = 1); primary efficacy analysis (N = 23)
Interventions	Each participant treated 1 migraine attack at home with oral sumatriptan (50 mg for a body surface area of 0.75-1.5 m^2 (~6-12 years of age) and 100 mg for a body surface area greater than 1.5 m^2 (~>12 years of age) and 1 migraine attack with placebo in a randomized order. Rescue medications were permitted at any time.
Outcomes	• Headache relief at 2 h (defined as a reduction in pain intensity by at least 50%) • Pain-free at 2 h • Use of rescue medication • Adverse events Other reported outcomes: • Pain intensity difference (pain intensity before drug minus pain intensity at assessment time) • Summed pain intensity difference (pain intensity difference times h elapsed from previous assessment • Treatment preference
Headache severity scale	100 mm VAS
Funding source	Arvo, Lea Ylppo Foundation, and Academy of Finland
Publication	Journal
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: no information provided
Allocation concealment (selection bias)	Unclear risk	Comment: no information provided
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "matching placebo. . . Each patient received two identical packages"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: missing outcome data balanced across intervention groups
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes were reported

Hämäläinen 1997c

Study characteristics	
Methods	Randomized, double-blind, placebo-controlled, 4-way cross-over trial of oral dihydroergotamine
Participants	Children or adolescents < 18 years with a diagnosis of migraine per IHS 1988 criteria and at least 2 migraine attacks per month. Most participants had participated in a previous trial of paracetamol and ibuprofen versus placebo. Randomized (N = 16); 1 medication used (N = 13); analyzed (N = 12)
Interventions	Dihydroergotamine (DHE) mesylate oral solution 2 mg/ml and placebo. Each participant treated 1 migraine attack at home with DHE 20 µg/kg (DHE solution 2 drops/10 kg) and 1 with placebo. If the first dose provided any relief, a second dose could be taken after 1 h. If neither treatment produced an adequate response, 1 further migraine attack was treated with DHE 40 µg/kg and 1 with placebo after contact with the investigator.
Outcomes	• Headache relief at 2 h (reduction of severe or moderate pain by at least 2 grades) • Pain-free at 2 h • Use of rescue medications • Adverse events Other reported outcomes: • Patient preference
Headache severity scale	5-point scale (5 severe, 3-4 moderate, 2 mild, 1 no pain)
Funding source	Not specified
Publication	Journal
Notes	—

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: no information provided
Allocation concealment (selection bias)	Unclear risk	Comment: no information provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "each patient received two identical bottles" Comment: the taste may have been different between the bottles
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: patients who were excluded were not described
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported

Hämäläinen 2002

Study characteristics	
Methods	Randomized, double-blind, placebo-controlled, single attack cross-over trial of sumatriptan nasal spray
Participants	Participants from 1 center in Germany were children 8-12 years of age with 6-month history of migraine with or without aura per IHS 1988 criteria, an attack frequency of 2-8 monthly, and minimum duration of 4 h. Randomized (N = 60); withdrawn (N = 3); intention-to-treat analysis and primary efficacy analysis (N = 59)
Interventions	Each participant treated 1 migraine attack with nasal sumatriptan (10 mg) or placebo nasal spray. The second migraine was treated with the other medication
Outcomes	• Headache relief at 2 h (2-point decrease in headache intensity) • Pain free at 2 h • Presence of nausea and vomiting at 2h • Use of rescue medication with 24 h • Adverse events Other reported outcomes: • Headache relief, pain free, nausea, vomiting, photophobia, and phonophobia at 15, 30, 60, 90, 180, and 240 minutes
Headache severity scale	4-point scale (none, mild, moderate, severe)
Funding source	GlaxoSmithKline
Publication	Clinical trial registry
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized at visit one". Comment: probably done as with previous studies by sponsor but not reported
Allocation concealment (selection bias)	Unclear risk	Quote: "randomized at visit one and received a single dose of sumatriptan 10 mg nasal spray or placebo to treat one migraine attack. At visit 2 they received the alternate treatment. . ."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Comment: no information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: missing outcome data balanced across intervention groups
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported

Lewis 2002

Study characteristics	
Methods	Randomized, double-blind, placebo-controlled, parallel-group trial of oral ibuprofen
Participants	Participants were 6-12 years of age and met diagnostic criteria for migraine without aura per revised IHS 1988 criteria for children (Winner 1995) from multiple sites in the United States. Enrolled (N = 138); treated/completed diary (N = 84)
Interventions	Each participant treated 1 migraine with liquid ibuprofen suspension (7.5 mg/kg) or placebo
Outcomes	• Headache relief (defined as a reduction from moderate or severe to mild or no headache) at 2 h • Pain-free at 2 h • Presence of nausea or vomiting at 2 h • Headache recurrence from 4 to 24 h • Use of rescue medication within 4 h • Adverse events Other reported outcomes: • Presence of photophobia or phonophobia at 2 h • Time to response with other time points (30, 60, 90, 180, and 240 min)
Headache severity scale	4-point scale (none, mild, moderate, severe)
Funding source	Not specified
Publication	Journal
Notes	—

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Subjects were randomly assigned (stratified by gender) to the study medication in a double-blind fashion."
Allocation concealment (selection bias)	Unclear risk	Quote: "Subjects were randomized to one of the following groups in a 1:1 ratio"
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "matching placebo suspension" Comment: no description of taste or color
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Fifty-four patients were randomized but were not evaluable. . . Six treated with study agent" Comment: missing outcome data balanced between intervention groups
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes were reported

Lewis 2007

Study characteristics	
Methods	Multicenter, randomized, double-blind, placebo-controlled, 2-way, 2-attack, cross-over study of zolmitriptan nasal spray with a single-blind 'placebo challenge' or 'enrichment' phase
Participants	Adolescents of age 12-17 years with a diagnosis of migraine with or without aura per the IHS 1988 criteria or revised IHS-1988 criteria (Winner 1995) with a frequency of 2 or more migraine attacks per month during the school year and < 14 days per month without migraine for the 3 months before screening. The usual duration of untreated migraine was required to be > 2 h. Participants were permitted to use preventive medication that had been stable for 2 months before randomization. Randomized (N = 248); withdrawn (N = 34); placebo responder to both attacks (N = 12); placebo responder to 1 attack (N = 12); missing efficiency data (N = 19); intention-to-treat analysis (N = 171)
Interventions	Each participant treated 1 migraine attack with zolmitriptan 5 mg nasal spray and another with matching placebo within a 12-week period. Each attack was treated initially with placebo normal saline within 30 min after the headache reached moderate or severe intensity. If migraine intensity remained moderate or severe, then participants were randomly assigned to use zolmitriptan or matching placebo (1:1). A second dose of randomized treatment or approved escape medications were permitted 2 h after the first dose if moderate or severe pain persisted.
Outcomes	• Headache relief (decrease from moderate or severe to mild or no headache) at 2 h (1 h was used as the primary outcome in the study) • Pain-free at 2 h • Use of rescue medication • Presence of nausea • Use of rescue medications within 2 h • Adverse events Other reported outcomes: • Presence of photophobia and phonophobia • Other time points including 15, 30, 45, 60, and 90 min
Headache severity scale	4-point scale (none, mild, moderate, severe)
Funding source	AstraZeneca
Publication	Journal and clinical trial registry
Notes	—

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly assigned strictly sequentially"
Allocation concealment (selection bias)	Low risk	Quote: "double-blind randomization schedule (prepared by the study sponsor)"
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "matching placebo" Comment: unique study design with placebo challenge where all subjects initially received placebo in a single-blind (participant) fashion. Only those who did not respond were randomly assigned to active drug or placebo.

Lewis 2007 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: missing outcome data distributed evenly across intervention groups
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported

Linder 2008

Study characteristics	
Methods	Randomized, double-blind, placebo-controlled, parallel-group multicenter trial of oral almotriptan
Participants	Participants from the United States (81 sites), Argentina (6 sites), Colombia (3 sites), and Mexico (3 sites) diagnosed with migraine were aged 12-17 years (block randomization in 2 groups: 12-14 years and 15-17 years). The participants were required to have a > 1-year history of migraine with or without aura per the IHS 1988 criteria and a frequency of 1-6 moderate or severe attacks per month, lasting > 4 h without treatment and occurring at intervals of > 24 h for the 2 months prior to screening. Following a 30-day run-in period to document migraine severity and frequency, eligible participants were randomized 1:1:1:1 within the 2 age groups to treat 1 attack. Enrolled (N = 866); did not receive medication (N = 146); non-compliant (N = 6); safety analysis (N = 720); primary efficacy analysis (N = 714)
Interventions	Each participant treated 1 attack with either oral almotriptan (6.25 mg, 12.5 mg, or 25 mg) or placebo as soon as possible within 4 h after the onset of moderate to severe pain.
Outcomes	• Headache relief at 2 h (a decrease from moderate or severe pain intensity to mild or no pain) • Pain-free at 2 h • Presence of nausea at 2 h • Use of rescue medication within 2-24 h • Headache recurrence within 2-24 h • Adverse events Other reported outcomes: • Other time points (0.25, 0.5, 1, 1.5 h) • Presense of photophobia or phonophobia at 2 h • Sustained pain relief • Sustained pain-free
Headache severity scale	4-point scale (none, mild, moderate, severe)
Funding source	Janssen-Ortho LLC: Ortho-McNeil Neurologics, Inc.
Publication	Journal and clinical trial registry
Notes	—

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized 1:1:1:1 within 2 age groups"

Linder 2008 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Comment: each participant received 2 tablets of either study medication or placebo
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Comment: described as 'double-blind'. Previous studies by sponsor included acceptable blinding methods (e.g. Lewis 2007).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: missing outcome data balanced across intervention groups
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported

NCT01211145

Study characteristics	
Methods	Randomized, double-blind, placebo-controlled, parallel group trial of zolmitriptan nasal spray
Participants	Participants from 74 study sites worldwide were adolescents 12-17 years of age, diagnosed with migraine per IHS 1988 or revised IHS criteria (Winner 1995) and a history of at least 2 migraine attacks per month. Lack of response to single-blind placebo run-in period was also required. Randomized (N = 798); did not receive study drug (N = 141); analyzed (N = 584)
Interventions	Zolmitriptan 0.5, 2.5, 5 mg nasal spray
Outcomes	• Pain-free at 2 h • Headache relief (defined as decreased from severe or moderate to mild or none) at 2 h • Use of rescue medication during the first 24 h • Presense of nausea or vomiting at 2 h Other reported outcomes: • Presence of photophobia, phonophobia, nausea, or vomiting at 0.25, 1, 3, 4, and 24 h • Headache relief (defined as decreased from severe or moderate to mild or none and no use of rescue medication) at 0.25, 1, 3, 4, and 24 h • Pain-free at 0.25, 1, 3, 4, and 24 h
Headache severity scale	4-point scale (none, mild, moderate, severe)
Funding source	AstraZeneca
Publication	Clinical trial registry
Notes	At the interim futility analysis, the zolmitriptan 0.5 and 2.5 mg groups were declared futile, allocation discontinued, and not included in the efficacy analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "were randomized into the study to obtain 800 evaluable patients"

NCT01211145 *(Continued)*

		Comment: no description of randomization procedures provided
Allocation concealment (selection bias)	Unclear risk	Comment: no information provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Comment: study is described as blinded but no information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Of the 798 patients, 82.3% (657/798 patients) received study drug, 90.4% (721/798 patients) completed the study and 9.5% (76/798 patients) discontinued from the study. . . All patients received their assigned treatment. . . Overall, the most common reason for study discontinuation was eligibility criteria not fulfilled (6.6%, 53/798 patients). No patients discontinued due to AEs."
Selective reporting (reporting bias)	Unclear risk	Comment: a clinical study report synopsis was reported with limited data

Rothner 1997

Study characteristics	
Methods	Randomized, double-blind, placebo-controlled, parallel trial of oral naratriptan
Participants	Participants were from the United States (44 sites), aged 12-17 years with a 1-year history of migraine with or without aura as per the IHS 1988 criteria and had 1-8 migraine attacks per month of moderate to severe intensity during the 2 months preceding the screening visit. Randomized (N = 350); withdrawn (N = 51); intention-to-treat and primary efficacy analysis (N = 300)
Interventions	Each participant treated 1 migraine with oral naratriptan (0.25 mg, 1.0 mg, or 2.5 mg) or placebo. A second, identical dose was available (optional) for participants who experienced recurrence.
Outcomes	• Headache relief at 2 h (reduction in pain severity from moderate or severe to none or mild); study primary outcome was at 4 h • Pain-free at 2 h • Use of rescue medication within 24 h • Presence of nausea at 2 h • Headache recurrence • Adverse events Other reported outcomes: • Headache relief at 15, 30, 45, 60, 90, and 180 minutes • Pain-free at 15, 30, 45, 60, 90, 180, and 240 minutes • Presence of nausea, photophobia, phonophobia at 15, 30, 45, 60, 90, 180, and 240 minutes • Sum of pain intensity scores • Sustained headache relief within 4-24 h • Clinical disability at 15, 30, 45, 60, 90, 120, 180, and 240 minutes • Sum of clinical disability intensity differences • Incidence of and time to meaningful relief within 240 minutes
Headache severity scale	4-point scale (none, mild, moderate, severe)

Rothner 1997 *(Continued)*

Funding source	GlaxoSmithKline
Publication	Abstract and clinical trial registry
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Subjects were randomized (1:1:1:1)"
Allocation concealment (selection bias)	Unclear risk	Comment: no information provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Comment: described as double-blind and previous studies by sponsor had acceptable blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: missing outcome data balanced across intervention groups
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported

Rothner 1999a

Study characteristics

Methods	Randomized, double-blind, placebo-controlled, parallel-group 3-attack trial of oral sumatriptan
Participants	Participants from 62 centers in 7 countries were 12-17 years of age with a minimum 6-month history of migraine with or without aura per IHS 1988 criteria and 1-6 attacks per month Randomized (N = 347); withdrawn (N = 117); intention-to-treat and primary efficacy analysis (N = 273)
Interventions	Each participant treated 1 migraine with oral sumatriptan 25 mg, 50 mg, 100 mg, or placebo. No maximum time after the onset of migraine was specified.
Outcomes	• Headache relief at 2 h (moderate or severe pain intensity reduced to no or mild pain) • Pain free at 2 h • Presence of nausea within 4 h • Use of rescue medication within 24 h • Recurrence of migraine within 4-24 h • Adverse events Other reported outcomes: • Presense of photophobia or phonophobia within 4 h • Other time points (headache relief at 1 h was primary outcome in study) • Time to meaningful relief
Headache severity scale	4-point scale (none, mild, moderate, severe)

Rothner 1999a *(Continued)*

Funding source	GlaxoSmithKline
Publication	Abstract and clinical trial registry
Notes	Headache alleviation: reduction in headache from grade 3 or 2 to grade 1 or 0 within 2 h where 3 = headache, I can't do anything; 2 = headache, I can do easy activities; 1 = headache, I can carry on as usual; and 0 = no headache. Funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: described as randomized but no details
Allocation concealment (selection bias)	Unclear risk	Comment: no description of allocation concealment
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Comment: no description of efforts to maintain blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: missing outcome data balanced across intervention groups
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported

Rothner 1999b

Study characteristics

Methods	Randomized, double-blind, placebo-controlled, parallel-group trial of oral sumatriptan
Participants	Participants from Canada (14 sites) were aged 12-17 years, had a 3-month history of migraine with or without aura as per the IHS 1988 criteria (except headaches could be < 2 h) and the migraine attack had lasted < 24 h. Randomized (N = 119); withdrawn (N = 27); intention-to-treat and primary efficacy analysis (N = 92)
Interventions	Each participant treated 1 migraine with oral sumatriptan (50 mg for body weight 30-50kg; 100 mg for body weight > 50kg) or placebo. Use of rescue medication was permitted after 4 h of study treatment.
Outcomes	• Headache relief at 2 h (2-grade decrease in headache disability) • Pain free at 2 h • Presence of nausea • Use of rescue medication after 4 h • Headache recurrence within 24 h • Adverse events Other reported outcomes: • 4 h time point • Presense of photophobia or phonophobia

Rothner 1999b *(Continued)*

	• Clinical disability • Time to start of headache improvement • Time to return to normal activities • Time until completely back to normal
Headache severity scale	4-point scale (none, mild, moderate, severe)
Funding source	GlaxoSmithKline
Publication	Abstract and clinical trial registry
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Subjects were randomized (1:1:1 ratio) to receive. . ."
Allocation concealment (selection bias)	Unclear risk	Comment: no information provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Comment: described as "placebo-controlled"; participant-reported outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: missing outcome data balanced across intervention groups.
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported

Rothner 1999c

Study characteristics	
Methods	Randomized, double-blind, placebo-controlled, parallel-group trial of oral sumatriptan
Participants	Participants were from 18 centers in 8 countries and 12-17 years of age with migraine with or without aura per IHS 1988 criteria; treated 1 attack following a run-in period of up to 8 weeks during which their usual medication was used to treat 1 migraine attack Randomized (N = 139); withdrawn (N = 37); intention-to-treat and primary efficacy analysis (N = 102)
Interventions	Oral sumatriptan 50 mg (30 to 50 kg) or sumatriptan 100 mg (> 50 kg) versus placebo
Outcomes	• Headache/disability relief (grade 2/3 to 0/1) at 2 h • Pain free at 2 h • Presence of nausea • Use of rescue medication after 4 h • Headache recurrence within 24 h • Adverse events

Rothner 1999c *(Continued)*

	Other reported outcomes: • 4 h time point • Presense of photophobia or phonophobia • Time to headache improvement • Time to disappearance of headache • Time to resumption of normal activities • Time to feeling 'completely back to normal' • Global response to study medication
Headache severity scale	Headache/clinical disability score (grade 3 = headache - "I can't do anything"; grade 2 = headache – "I can do easy activities"; grade 1 = headache – "I can carry on as usual", grade 0 = no headache)
Funding source	GlaxoSmithKline
Publication	Abstract and clinical trial registry
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: described as "randomized in a 1:1:1 ratio. . ."
Allocation concealment (selection bias)	Unclear risk	Comment: no description of methods to maintain allocation concealment
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Comment: described as "double-blind"; previous studies by sponsor had adequate blinding procedures
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: withdrawals balances between intervention groups
Selective reporting (reporting bias)	Unclear risk	Comment: outcomes extensively reported in the GlaxoSmithKline clinical trial registry

Rothner 2006

Study characteristics

Methods	Randomized, double-blind, placebo-controlled, parallel-group trial of oral zolmitriptan
Participants	Participants were from the United States (40 sites), Canada (10 sites), India (23 sites), Finland, Germany, and the United Kingdom. Eligible participants were aged 12-17 years with a diagnosis of migraine with or without aura per the IHS 1988 criteria and were required to have 2-10 migraine or non-migraine headaches per month lasting longer than 4 h without treatment in the last 3 months preceding screening Randomized (N = 850); did not treat at least 1 attack (N = 151); intention-to-treat and primary efficacy analysis (N = 696)

Rothner 2006 *(Continued)*

Interventions	Each participant treated 1 migraine attack with oral zolmitriptan (2.5 mg, 5 mg, or 10 mg) or placebo no later than 1 h after the onset of moderate or severe headache, more than 24 h had elapsed since the last migraine attack and the migraine attack occurred within 12 weeks of randomization. Participants were allowed to take an approved escape medication 2 or more h after study treatment.
Outcomes	• Headache relief at 2 h (pain decrease from moderate or severe to mild or none) • Pain free • Adverse events Other reported outcomes: • Other time points including 30 and 60 min
Headache severity scale	4-point scale (none, mild, moderate, severe)
Funding source	AstraZeneca
Publication	Journal and clinical trial registry
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "numbers allocated sequentially as patients entered the study"
Allocation concealment (selection bias)	Unclear risk	Quote: "The randomization schedule was produced by the Biometrics Group of AstraZeneca."
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "three tablets, all of which were identical in appearance"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: missing outcome data balanced across intervention groups
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported

Ueberall 1999

Study characteristics

Methods	Randomized, double-blind, placebo-controlled, 2-way cross-over trial of intranasal sumatriptan
Participants	Participants were < 10 years of age with migraine with or without aura per IHS 1988 criteria and at least 2 migraine attacks per month Randomized (N = 14); analyzed (N = 14)
Interventions	Each participant treated 1 migraine with intranasal sumatriptan (20 mg) or placebo. The second migraine was treated with the other medication.

Ueberall 1999 *(Continued)*

Outcomes	• Headache relief at 2 h • Pain free at 2 h • Headache recurrence • Use of rescue medication • Presence of nausea or vomiting within 4 h • Adverse events Other reported outcomes: • Presense of photophobia or phonophobia within 4 h • Other time points (30, 60, 180, 240 minutes) • Time to meaningful recovery • Treatment preference
Headache severity scale	4-point scale (none, mild, moderate, severe)
Funding source	Not specified
Publication	Journal
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was based on a computer algorithm. . ."
Allocation concealment (selection bias)	Unclear risk	Quote: "Patients were randomly assigned to two alternative treatment strata"; "access to treatment assignments were given to D.W., if necessary"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "0.9% sodium chloride" used as placebo Comment: cross-over trial; blinding likely maintained. Disturbance of taste reported both for sumatriptan and placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Data sufficient for analysis were provided by all 14 children".
Selective reporting (reporting bias)	Low risk	Comment: all outcomes reported

Visser 2004a

Study characteristics

Methods	Randomized, double-blind, placebo-controlled, parallel-group single-attack trial of oral rizatriptan
Participants	Participants from 44 centers in the United States 12-17 years of age with a 1 year history of migraine with or without aura per IHS 1988 criteria and 1-8 attacks per month. Randomization was stratified by age (12-14 and 15-17 years). Randomized (N = 686); did not take study medication (N = 210); primary efficacy analysis (N = 476)

Visser 2004a *(Continued)*

Interventions	Each participant treated 1 migraine with oral rizatriptan (5 mg) or placebo within 30 minutes of onset. Up to 2 recurrences could be treated with the same medication. Participants could only treat migraine attacks on days they were not in school or at camp.
Outcomes	• Headache relief at 2 h (reduction from moderate or severe to mild or none) • Pain free at 2 h • Headache recurrence within 24 h • Presence of nausea or vomiting • Adverse events Other reported outcomes: • Presense of photophobia or phonophobia • Other time points (0.5, 1, 1.5, 3, and 4 h), • Functional ability • Headache severity
Headache severity scale	4-level (none, mild, moderate, severe)
Funding source	Merck
Publication	Journal
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: no information provided
Allocation concealment (selection bias)	Unclear risk	Comment: no information provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Comment: described as double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "The number of patients who discontinued prior to taking study medication and the distribution of reasons for the lack of treatment were comparable across the treatment arms."
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported

Winner 1997

Study characteristics	
Methods	Randomized, double-blind, placebo-controlled, 4-period, outpatient, cross-over, 4-attack study of oral sumatriptan
Participants	Participants were 12-17 yrs with > 6 month history of migraine with or without aura as defined by IHS 1988; had 1-8 moderate or severe migraine attacks monthly during the 2 months prior to screening

Winner 1997 *(Continued)*

	Randomized (N = 355); withdrawn (N = 194); intention-to-treat and primary efficacy analysis (N = 298)
Interventions	Each participant treated up to 4 migraine attacks of moderate or severe intensity in a cross-over fashion; 1 attack with placebo and 3 with sumatriptan 25 mg, 50 mg, or 100 mg (same dose for all 3 attacks). Participants were randomized in a balanced fashion to 1-12 treatment sequences.
Outcomes	• Headache relief (reduction in severity from moderate or severe to none or mild) at 2 h after the first dose of study drug for the first attack and across attacks were the primary outcome measures; data from treatment of the first migraine attack are used in the systematic review • Pain-free at 2 h • Presense of nausea or vomiting at 2 h • Use of rescue medication • Adverse events Other reported outcomes: • Time to meaningful relief (within 4 h) • Presense of photophobia or phonophobia • Clinical disability • Other time points (15, 30, 45, 60, 90, 180, and 240 min)
Headache severity scale	4-level (none, mild, moderate, severe)
Funding source	GlaxoSmithKline
Publication	Journal and clinical trial registry
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: described as "randomized in a balanced manner to 1 of 12 treatment sequences"
Allocation concealment (selection bias)	Unclear risk	Comment: methods to maintain allocation concealment were not described; previous studies by sponsor had adequate allocation concealment
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Comment: described as "double-blind, placebo-controlled"; methods to maintain blinding were not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: a total of 194 subjects withdrew, but were balanced across intervention groups
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported

Winner 2000

Study characteristics

Winner 2000 *(Continued)*

Methods	Randomized, double-blind, placebo-controlled, single-attack, parallel-group study of intranasal sumatriptan
Participants	Males and females 12-17 years of age with a diagnosis of migraine (with or without aura) meeting IHS 1988 criteria and typical duration > 4 h and with at least a 6-month history of 2-8 moderate or severe migraine attacks per month for each of the 2 months preceding study enrolment. Participants were required to have < 15 days of tension headache per month and were required to have failed at least 1 previous over-the-counter or prescription medication for the treatment of migraine. Randomized (N = 653); withdrawn (N = 147); missing efficacy data (N = 3); intention-to-treat analysis (N = 510); primary efficacy analysis (N = 507)
Interventions	Each participant treated 1 migraine with nasal sumatriptan (5, 10, or 20 mg) or placebo. A second dose of the same nasal spray could be used 2-24 h after the initial dose.
Outcomes	• Headache relief at 2 h (reduction from moderate or severe to mild or no pain) • Pain-free at 2 h • Headache recurrence (from 2 to 24 h) • Rescue medication (from 2 to 24 h) • Associated symptoms (nausea, vomiting) (within 2 h) • Adverse events Other reported outcomes: • Photophobia or phonophobia within 2 h
Headache severity scale	4-level (none, mild, moderate, severe)
Funding source	GlaxoSmithKline
Publication	Journal and clinical trial registry
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomized after successful screening using a computer-generated, parallel-group design, 1:1:1:1 ratio (block size of 8)"
Allocation concealment (selection bias)	Low risk	Quote: "The allocation schedule was concealed in tamper-evident, blinded envelopes kept by the sponsor"
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "identically appearing placebo"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: missing outcome data balanced across intervention groups
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported

Winner 2002

Study characteristics	
Methods	Randomized, double-blind, placebo-controlled, parallel-group trial of oral rizatriptan
Participants	Participants were 12-17 yrs, with an average of at least 1 but no more than 8 migraines per IHS 1988 criteria and stratified in 2 groups: 12-14 years and 15-17 years. Efforts were made to enrol equal numbers in each age group. Randomized (N = 360); did not receive study medication (N = 64); primary efficacy analysis (N = 296)
Interventions	Each participant was instructed to take the study medication (rizatriptan 5 mg or placebo) within 30 min of onset of a moderate or severe migraine
Outcomes	• Pain-free at 2 h • Headache relief (reduction in pain to mild or none) at 2 h • Presence of nausea • Use of rescue medication • Headache recurrence (within 24 h) • Adverse events Other reported outcomes: • Presence of photophobia or phonophobia • Functional disability
Headache severity scale	4-level (none, mild, moderate, severe)
Funding source	Merck
Publication	Journal
Notes	—

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly assigned"
Allocation concealment (selection bias)	Unclear risk	Comment: no information provided.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Comment: no information provided
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: small imbalance of missing outcome data in the placebo group (N = 6 vs N = 1)
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported

Winner 2006

Study characteristics	
Methods	Randomized, double-blind, placebo-controlled, parallel-group, multicenter, single-attack, outpatient study of intranasal sumatriptan
Participants	Participants were 12-17 years of age; had a history of migraine of at least 6 months duration (with or without aura) in accordance with IHS 1988; had at least 1-8 moderate or severe migraine attacks per month in each of the 2 months before study enrolment; and were able to distinguish migraine attacks as discrete attacks, separate from other headaches (i.e., tension headaches) Randomized (N = 888); did not receive study medication (N = 150); withdrawn (N = 7); intention-to-treat and primary efficacy analysis (N = 731)
Interventions	Sumatriptan 5 mg nasal spray; sumatriptan 20 mg nasal spray; or placebo
Outcomes	• Headache relief at 2 h (grade 2 or 3 reduced to 0 or 1) (relief at 1 h was the study primary outcome) • Pain-free • Presense of nausea • Use of rescue medications (within 24 h) • Headache recurrence (within 24 h) • Adverse events Other reported outcomes: • Sustained pain-freedom to 24 h • Sustained headache relief from 2-24 h • Presence of photophobia or phonophobia (within 2 h)
Headache severity scale	4-level (none, mild, moderate, severe)
Funding source	GlaxoSmithKline
Publication	Journal and clinical trial registry
Notes	—

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "randomized in a 1:1:1 ratio (in blocks of six) to one of three treatment groups"; "computer-generated randomization schedule" Comment: previous migraine studies by GlaxoSmithKline have documented acceptable sequence generation (e.g. Winner 2000)
Allocation concealment (selection bias)	Low risk	Quote: "randomization schedule prepared by the sponsor" Comment: centralized allocation
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "[nasal spray] devices for active drug and placebo were identical in appearance and construction to maintain the study blind."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all withdrawal documented in a flow diagram

Winner 2006 *(Continued)*

Selective reporting (reporting bias)	Low risk	Comment: missing outcome data balanced across intervention groups

Winner 2007

Study characteristics	
Methods	Randomized, double-blind, parallel-group, placebo-controlled trial of oral eletriptan
Participants	Participants were 12-17 years, met ICHD-2 criteria for migraine with or without aura, and suffered at least 1 migraine attack every 6 weeks. Mean migraine duration was required to be a minimum of 4 h. Randomized (N = 348); did not receive study medication (N = 74); intention-to-treat and primary efficacy analysis (N = 274)
Interventions	Eletriptan 40 mg PO, placebo taken within 4 h of headache onset
Outcomes	• Headache relief at 2 h (reduction from moderate or severe to mild or no pain) • Pain-free at 2 h • Presense of nausea • Use of rescue medications (within 24 h) • Headache recurrence (within 2 to 24 h) • Adverse events Other reported outcomes: • Headache relief and pain-free at 1 h • Presence of photophobia or phonophobia • Change in functional impairment • Migraine-free (no headache and no associated symptoms at 2 h • Acceptability of medication
Headache severity scale	4-level (none, mild, moderate, severe)
Funding source	Pfizer
Publication	Journal
Notes	—

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: no information provided
Allocation concealment (selection bias)	Unclear risk	Comment: no information provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Comment: described as "placebo-controlled", but no other description

Winner 2007 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Three hundred and eighty-four were screened, of whom 348 were randomized to study drug . . ."; "Seventy-four were randomized but did not take the study drug: (1) 35 did not treat a migraine attack during the 12-week time window. . ." Comment: withdrawals balanced across intervention groups
Selective reporting (reporting bias)	Low risk	Comment: all expected outcomes reported; originally published as an abstract in 2000 (Pitman 2000) followed by this full report.

AE: adverse events; **DHE**: dihydroergotamine; **LOCF**: last observation carried forward; **PO**: per os (by mouth); **VAS**: visual analogue scale.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Brousseau 2004	The Emergency Department setting and parenteral interventions studied (intravenous prochlorperazine versus ketorolac) were significantly different from included clinical trials of interventions in the outpatient setting. As there were few other clinical trials in the Emergency Department setting, we made a post hoc decision to exclude this study to simplify the review conclusions.
Cady 2011	Non-drug clinical trial and participants were not exclusively pediatric
Gertsch 2011	Open-label, uncontrolled study
NCT00355394	The Emergency Department setting and parenteral intervention studied (intravenous metoclopramide) was significantly different from included clinical trials of interventions in the outpatient setting. As there were few other clinical trials in the Emergency Department setting, we made a post hoc decision to exclude this study to simplify the review conclusions.
Soriani 2001	A non-placebo-controlled randomized study comparing paracetamol and nimesulide. Each of 60 participants in the study treated 10 attacks, and the primary outcome of headache relief was reported as a percentage of attacks. No individual participant data was reported so was not included in the meta-analysis.
SUM40090	Open-label, uncontrolled study
Trautmann 2010	Non-drug clinical trial
Winner 2011	Study of rapid disintegrating formulation of sumatriptan was not a randomized controlled trial

Characteristics of studies awaiting classification *[ordered by study ID]*

Winner 2015

Methods	Randomized, placebo-controlled, double-blind cross-over trial of oral sumatriptan + naproxen sodium
Participants	Male and female adolescents 12-17 years of age meeting ICHD-2 criteria with an average of at least 1 but no more than 8 migraines per month in the previous 6 months Enrolled (N = 104); did not receive study medication (N = 10); primary efficacy analysis (N = 94)

Winner 2015 *(Continued)*

Interventions	Sumatriptan + naproxen sodium 85 mg + 500 mg; or placebo for the treatment of 4 migraine attacks (3 active, 1 placebo)
Outcomes	• Pain freedom at 2 h (post-treatment pain severity of 0 with no use of rescue medication) • Presense of nausea or vomiting • Use of rescue medications (within 24 h) • Headache recurrence from 2-24 h • Adverse event Other reported outcomes: • Presence of photophobia or phonophobia
Notes	—

DATA AND ANALYSES

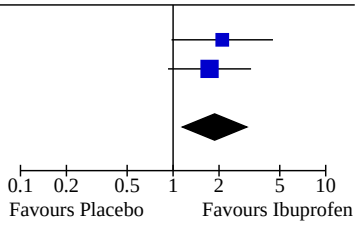
Comparison 1. Ibuprofen vs placebo in children

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Pain-free	2	125	Risk Ratio (M-H, Random, 95% CI)	1.87 [1.15, 3.04]
1.2 Adverse events (any)	1	80	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.13, 0.13]
1.3 Headache relief	2	125	Risk Ratio (M-H, Random, 95% CI)	1.49 [1.11, 2.00]
1.4 Rescue medication	2	164	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.02, 1.56]
1.5 Headache recurrence	1	38	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.01, 5.68]

Analysis 1.1. Comparison 1: Ibuprofen vs placebo in children, Outcome 1: Pain-free

Study or Subgroup	Ibuprofen Events	Ibuprofen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Hämäläinen 1997a	12	20	6	21	40.1%	2.10 [0.98 , 4.51]
Lewis 2002	20	45	10	39	59.9%	1.73 [0.93 , 3.24]
Total (95% CI)		**65**		**60**	**100.0%**	**1.87 [1.15 , 3.04]**
Total events:	32		16			

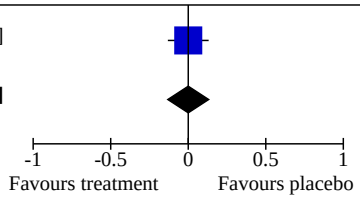
Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 1 (P = 0.70); I² = 0%
Test for overall effect: Z = 2.54 (P = 0.01)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Ibuprofen vs placebo in children, Outcome 2: Adverse events (any)

Study or Subgroup	Ibuprofen Events	Ibuprofen Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
Hämäläinen 1997a	4	40	4	40	100.0%	0.00 [-0.13 , 0.13]
Total (95% CI)		**40**		**40**	**100.0%**	**0.00 [-0.13 , 0.13]**
Total events:	4		4			

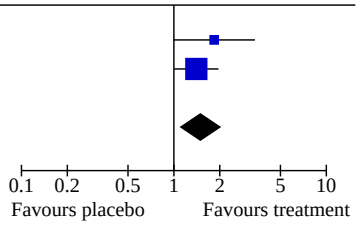
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: Ibuprofen vs placebo in children, Outcome 3: Headache relief

Study or Subgroup	Ibuprofen Events	Ibuprofen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Hämäläinen 1997a	14	20	8	21	22.8%	1.84 [0.99 , 3.40]
Lewis 2002	34	45	21	39	77.2%	1.40 [1.00 , 1.96]
Total (95% CI)		**65**		**60**	**100.0%**	**1.49 [1.11 , 2.00]**
Total events:	48		29			

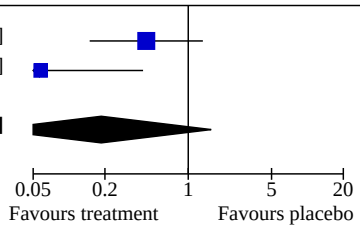
Heterogeneity: Tau² = 0.00; Chi² = 0.58, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 2.67 (P = 0.008)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: Ibuprofen vs placebo in children, Outcome 4: Rescue medication

Study or Subgroup	Ibuprofen Events	Ibuprofen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Hämäläinen 1997a	4	40	9	40	57.4%	0.44 [0.15 , 1.33]
Lewis 2002	1	45	15	39	42.6%	0.06 [0.01 , 0.42]
Total (95% CI)		**85**		**79**	**100.0%**	**0.19 [0.02 , 1.56]**
Total events:	5		24			

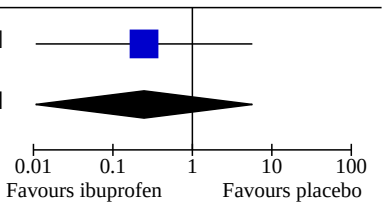
Heterogeneity: Tau² = 1.74; Chi² = 3.61, df = 1 (P = 0.06); I² = 72%
Test for overall effect: Z = 1.55 (P = 0.12)
Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1: Ibuprofen vs placebo in children, Outcome 5: Headache recurrence

Study or Subgroup	Ibuprofen Events	Ibuprofen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hämäläinen 1997a	0	22	1	16	100.0%	0.25 [0.01 , 5.68]
Total (95% CI)		**22**		**16**	**100.0%**	**0.25 [0.01 , 5.68]**
Total events:	0		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.87 (P = 0.38)
Test for subgroup differences: Not applicable

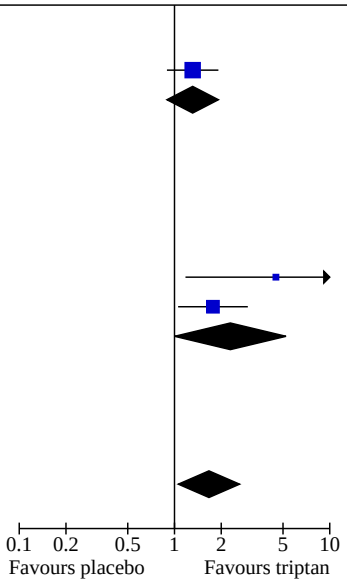


Comparison 2. Triptans vs placebo in children

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Pain-free	3	345	Risk Ratio (M-H, Random, 95% CI)	1.67 [1.06, 2.62]
2.1.1 Rizatriptan	1	200	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.89, 1.92]
2.1.2 Sumatriptan	2	145	Risk Ratio (M-H, Random, 95% CI)	2.29 [1.00, 5.23]
2.2 Adverse events (any)	3	420	Risk Difference (M-H, Random, 95% CI)	0.06 [-0.04, 0.17]
2.2.1 Rizatriptan	1	275	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.09, 0.09]
2.2.2 Sumatriptan	2	145	Risk Difference (M-H, Random, 95% CI)	0.13 [0.01, 0.26]
2.3 Headache relief	3	345	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.88, 2.08]
2.3.1 Rizatriptan	1	200	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.75, 1.24]
2.3.2 Sumatriptan	2	145	Risk Ratio (M-H, Random, 95% CI)	1.65 [1.21, 2.26]
2.4 Rescue medication	2	145	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.06, 1.45]
2.4.1 Sumatriptan	2	145	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.06, 1.45]
2.5 Headache recurrence	1	18	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.5.1 Sumatriptan	1	18	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.6 Presence of nausea	3	345	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.46, 0.90]
2.6.1 Rizatriptan	1	200	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.38, 1.22]
2.6.2 Sumatriptan	2	145	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.42, 0.94]
2.7 Presence of vomiting	3	345	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.13, 1.86]
2.7.1 Rizatriptan	1	200	Risk Ratio (M-H, Random, 95% CI)	1.73 [0.43, 7.06]
2.7.2 Sumatriptan	2	145	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.09, 0.99]

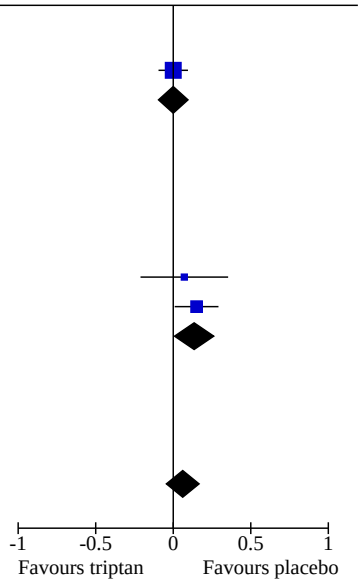
Analysis 2.1. Comparison 2: Triptans vs placebo in children, Outcome 1: Pain-free

Study or Subgroup	Triptan Events	Triptan Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Rizatriptan						
Ho 2012	39	98	31	102	50.9%	1.31 [0.89 , 1.92]
Subtotal (95% CI)		**98**		**102**	**50.9%**	**1.31 [0.89 , 1.92]**
Total events:	39		31			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.38 (P = 0.17)						
2.1.2 Sumatriptan						
Ueberall 1999	9	14	2	14	10.0%	4.50 [1.18 , 17.21]
Hämäläinen 2002	27	59	15	58	39.1%	1.77 [1.06 , 2.97]
Subtotal (95% CI)		**73**		**72**	**49.1%**	**2.29 [1.00 , 5.23]**
Total events:	36		17			
Heterogeneity: Tau² = 0.18; Chi² = 1.65, df = 1 (P = 0.20); I² = 40%						
Test for overall effect: Z = 1.97 (P = 0.05)						
Total (95% CI)		**171**		**174**	**100.0%**	**1.67 [1.06 , 2.62]**
Total events:	75		48			
Heterogeneity: Tau² = 0.07; Chi² = 3.47, df = 2 (P = 0.18); I² = 42%						
Test for overall effect: Z = 2.21 (P = 0.03)						
Test for subgroup differences: Chi² = 1.45, df = 1 (P = 0.23), I² = 30.9%						



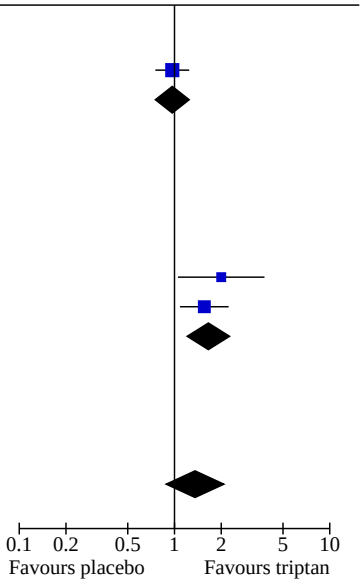
Analysis 2.2. Comparison 2: Triptans vs placebo in children, Outcome 2: Adverse events (any)

Study or Subgroup	Triptan Events	Triptan Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
2.2.1 Rizatriptan						
Ho 2012	25	125	30	150	53.0%	0.00 [-0.09 , 0.09]
Subtotal (95% CI)		**125**		**150**	**53.0%**	**0.00 [-0.09 , 0.09]**
Total events:	25		30			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
2.2.2 Sumatriptan						
Ueberall 1999	3	14	2	14	12.1%	0.07 [-0.21 , 0.35]
Hämäläinen 2002	16	59	7	58	34.9%	0.15 [0.01 , 0.29]
Subtotal (95% CI)		**73**		**72**	**47.0%**	**0.13 [0.01 , 0.26]**
Total events:	19		9			
Heterogeneity: Tau² = 0.00; Chi² = 0.24, df = 1 (P = 0.62); I² = 0%						
Test for overall effect: Z = 2.09 (P = 0.04)						
Total (95% CI)		**198**		**222**	**100.0%**	**0.06 [-0.04 , 0.17]**
Total events:	44		39			
Heterogeneity: Tau² = 0.00; Chi² = 3.04, df = 2 (P = 0.22); I² = 34%						
Test for overall effect: Z = 1.14 (P = 0.26)						
Test for subgroup differences: Chi² = 2.80, df = 1 (P = 0.09), I² = 64.2%						



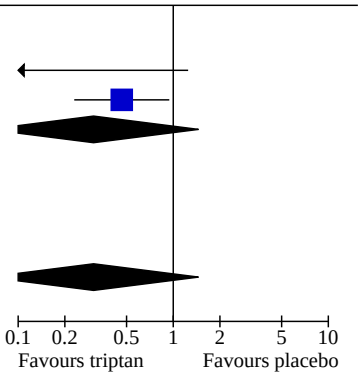
Analysis 2.3. Comparison 2: Triptans vs placebo in children, Outcome 3: Headache relief

Study or Subgroup	Triptan Events	Triptan Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.3.1 Rizatriptan						
Ho 2012	53	98	57	102	41.2%	0.97 [0.75 , 1.24]
Subtotal (95% CI)		**98**		**102**	**41.2%**	**0.97 [0.75 , 1.24]**
Total events:	53		57			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.26 (P = 0.80)						
2.3.2 Sumatriptan						
Ueberall 1999	12	14	6	14	23.1%	2.00 [1.05 , 3.80]
Hämäläinen 2002	38	59	24	58	35.8%	1.56 [1.09 , 2.23]
Subtotal (95% CI)		**73**		**72**	**58.8%**	**1.65 [1.21 , 2.26]**
Total events:	50		30			
Heterogeneity: Tau² = 0.00; Chi² = 0.45, df = 1 (P = 0.50); I² = 0%						
Test for overall effect: Z = 3.14 (P = 0.002)						
Total (95% CI)		**171**		**174**	**100.0%**	**1.36 [0.88 , 2.08]**
Total events:	103		87			
Heterogeneity: Tau² = 0.10; Chi² = 7.27, df = 2 (P = 0.03); I² = 72%						
Test for overall effect: Z = 1.40 (P = 0.16)						
Test for subgroup differences: Chi² = 6.81, df = 1 (P = 0.009), I² = 85.3%						



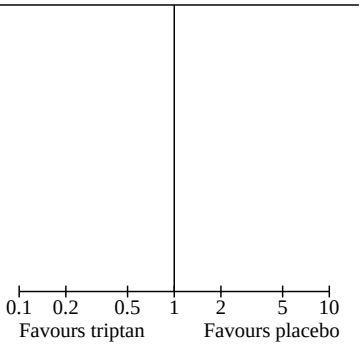
Analysis 2.4. Comparison 2: Triptans vs placebo in children, Outcome 4: Rescue medication

Study or Subgroup	Triptan Events	Triptan Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.4.1 Sumatriptan						
Ueberall 1999	0	14	6	14	23.3%	0.08 [0.00 , 1.25]
Hämäläinen 2002	9	59	19	58	76.7%	0.47 [0.23 , 0.94]
Subtotal (95% CI)		**73**		**72**	**100.0%**	**0.31 [0.06 , 1.45]**
Total events:	9		25			
Heterogeneity: Tau² = 0.69; Chi² = 1.64, df = 1 (P = 0.20); I² = 39%						
Test for overall effect: Z = 1.49 (P = 0.14)						
Total (95% CI)		**73**		**72**	**100.0%**	**0.31 [0.06 , 1.45]**
Total events:	9		25			
Heterogeneity: Tau² = 0.69; Chi² = 1.64, df = 1 (P = 0.20); I² = 39%						
Test for overall effect: Z = 1.49 (P = 0.14)						
Test for subgroup differences: Not applicable						



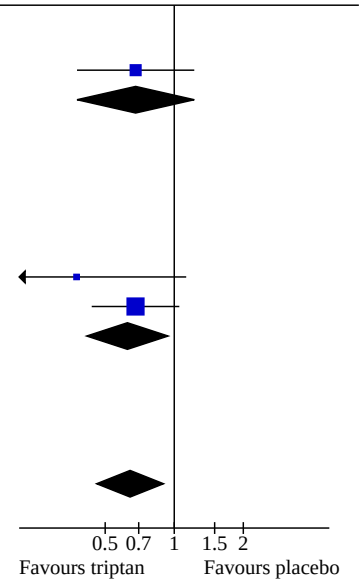
Analysis 2.5. Comparison 2: Triptans vs placebo in children, Outcome 5: Headache recurrence

Study or Subgroup	Triptan Events	Triptan Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.5.1 Sumatriptan						
Ueberall 1999	0	12	0	6		Not estimable
Subtotal (95% CI)		**12**		**6**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**12**		**6**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						

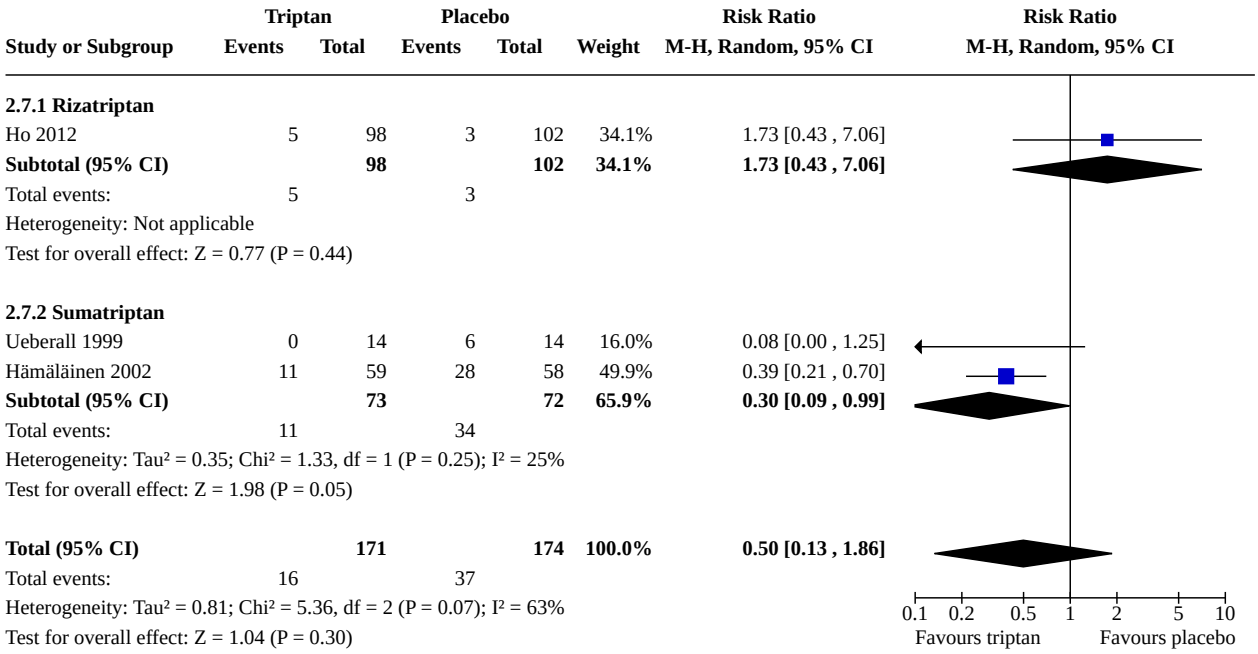


Analysis 2.6. Comparison 2: Triptans vs placebo in children, Outcome 6: Presence of nausea

Study or Subgroup	Triptan Events	Triptan Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.6.1 Rizatriptan						
Ho 2012	15	98	23	102	32.5%	0.68 [0.38 , 1.22]
Subtotal (95% CI)		**98**		**102**	**32.5%**	**0.68 [0.38 , 1.22]**
Total events:	15		23			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.29 (P = 0.20)						
2.6.2 Sumatriptan						
Ueberall 1999	3	14	8	14	9.3%	0.38 [0.12 , 1.13]
Hämäläinen 2002	20	59	29	58	58.2%	0.68 [0.44 , 1.05]
Subtotal (95% CI)		**73**		**72**	**67.5%**	**0.62 [0.42 , 0.94]**
Total events:	23		37			
Heterogeneity: Tau² = 0.00; Chi² = 0.97, df = 1 (P = 0.33); I² = 0%						
Test for overall effect: Z = 2.26 (P = 0.02)						
Total (95% CI)		**171**		**174**	**100.0%**	**0.64 [0.46 , 0.90]**
Total events:	38		60			
Heterogeneity: Tau² = 0.00; Chi² = 1.01, df = 2 (P = 0.60); I² = 0%						
Test for overall effect: Z = 2.59 (P = 0.010)						
Test for subgroup differences: Chi² = 0.05, df = 1 (P = 0.82), I² = 0%						



Analysis 2.7. Comparison 2: Triptans vs placebo in children, Outcome 7: Presence of vomiting



Comparison 3. Triptans vs placebo in adolescents

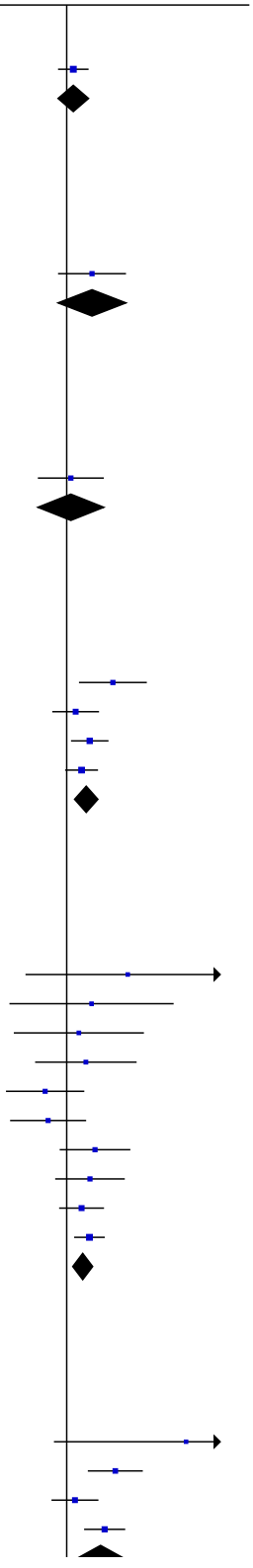
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Pain-free	21	6761	Risk Ratio (M-H, Random, 95% CI)	1.32 [1.19, 1.47]
3.1.1 Almotriptan	1	714	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.88, 1.39]
3.1.2 Eletriptan	1	274	Risk Ratio (M-H, Random, 95% CI)	1.46 [0.88, 2.43]
3.1.3 Naratriptan	1	300	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.65, 1.75]
3.1.4 Rizatriptan	4	1526	Risk Ratio (M-H, Random, 95% CI)	1.34 [1.13, 1.60]
3.1.5 Sumatriptan	10	2415	Risk Ratio (M-H, Random, 95% CI)	1.27 [1.10, 1.48]
3.1.6 Zolmitriptan	4	1532	Risk Ratio (M-H, Random, 95% CI)	1.66 [1.16, 2.38]
3.2 Adverse events (any)	21	7876	Risk Difference (M-H, Random, 95% CI)	0.13 [0.08, 0.18]
3.2.1 Almotriptan	1	720	Risk Difference (M-H, Random, 95% CI)	0.05 [0.00, 0.09]
3.2.2 Eletriptan	1	242	Risk Difference (M-H, Random, 95% CI)	0.14 [0.02, 0.26]
3.2.3 Naratriptan	1	300	Risk Difference (M-H, Random, 95% CI)	0.16 [0.05, 0.27]
3.2.4 Rizatriptan	4	1706	Risk Difference (M-H, Random, 95% CI)	0.04 [-0.02, 0.10]
3.2.5 Sumatriptan	10	2969	Risk Difference (M-H, Random, 95% CI)	0.18 [0.09, 0.27]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2.6 Zolmitriptan	4	1939	Risk Difference (M-H, Random, 95% CI)	0.14 [0.07, 0.20]
3.3 Headache relief	20	6182	Risk Ratio (M-H, Random, 95% CI)	1.14 [1.04, 1.24]
3.3.1 Almotriptan	1	714	Risk Ratio (M-H, Random, 95% CI)	1.27 [1.10, 1.47]
3.3.2 Eletriptan	1	277	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.79, 1.17]
3.3.3 Naratriptan	1	300	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.65, 1.00]
3.3.4 Rizatriptan	4	1526	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.99, 1.56]
3.3.5 Sumatriptan	10	2392	Risk Ratio (M-H, Random, 95% CI)	1.14 [1.02, 1.28]
3.3.6 Zolmitriptan	3	973	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.87, 1.69]
3.4 Rescue medication	18	5066	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.72, 0.87]
3.4.1 Almotriptan	1	714	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.28, 1.16]
3.4.2 Eletriptan	1	277	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.59, 1.12]
3.4.3 Naratriptan	1	300	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.55, 1.53]
3.4.4 Rizatriptan	3	956	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.55, 1.01]
3.4.5 Sumatriptan	10	2451	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.70, 0.92]
3.4.6 Zolmitriptan	2	368	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.20, 1.52]
3.5 Headache recurrence	15	2463	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.68, 0.93]
3.5.1 Almotriptan	1	477	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.44, 2.89]
3.5.2 Eletriptan	1	161	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.53, 1.23]
3.5.3 Naratriptan	1	201	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.42, 1.67]
3.5.4 Rizatriptan	1	177	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.30, 1.32]
3.5.5 Sumatriptan	9	1319	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.65, 0.94]
3.5.6 Zolmitriptan	2	128	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.36, 2.65]
3.6 Presence of nausea	17	4975	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.79, 1.12]
3.6.1 Almotriptan	1	356	Risk Ratio (M-H, Random, 95% CI)	1.45 [1.04, 2.02]
3.6.2 Eletriptan	1	277	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.84, 1.09]
3.6.3 Naratriptan	1	300	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.66, 1.78]
3.6.4 Rizatriptan	2	1060	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.49, 0.80]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.6.5 Sumatriptan	10	2279	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.78, 1.29]
3.6.6 Zolmitriptan	2	703	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.04, 4.02]
3.7 Presence of vomiting	12	4037	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.48, 1.12]
3.7.1 Almotriptan	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.7.2 Eletriptan	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.7.3 Naratriptan	1	300	Risk Ratio (M-H, Random, 95% CI)	1.96 [0.24, 16.05]
3.7.4 Rizatriptan	1	769	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.22, 1.18]
3.7.5 Sumatriptan	8	2265	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.39, 1.20]
3.7.6 Zolmitriptan	2	703	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.79, 1.58]

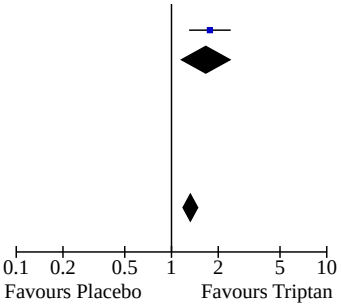
Analysis 3.1. Comparison 3: Triptans vs placebo in adolescents, Outcome 1: Pain-free

Study or Subgroup	Triptan Events	Triptan Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 Almotriptan						
Linder 2008	212	544	60	170	10.6%	1.10 [0.88 , 1.39]
Subtotal (95% CI)		**544**		**170**	**10.6%**	**1.10 [0.88 , 1.39]**
Total events:	212		60			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.85 (P = 0.40)						
3.1.2 Eletriptan						
Winner 2007	31	141	20	133	3.6%	1.46 [0.88 , 2.43]
Subtotal (95% CI)		**141**		**133**	**3.6%**	**1.46 [0.88 , 2.43]**
Total events:	31		20			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.46 (P = 0.14)						
3.1.3 Naratriptan						
Rothner 1997	52	226	16	74	3.8%	1.06 [0.65 , 1.75]
Subtotal (95% CI)		**226**		**74**	**3.8%**	**1.06 [0.65 , 1.75]**
Total events:	52		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.25 (P = 0.81)						
3.1.4 Rizatriptan						
Ahonen 2006	34	96	17	96	3.7%	2.00 [1.20 , 3.33]
Winner 2002	48	149	40	142	6.4%	1.14 [0.81 , 1.62]
Ho 2012	87	284	62	286	8.5%	1.41 [1.07 , 1.87]
Visser 2004a	91	233	75	240	9.8%	1.25 [0.98 , 1.60]
Subtotal (95% CI)		**762**		**764**	**28.4%**	**1.34 [1.13 , 1.60]**
Total events:	260		194			
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 3.61$, df = 3 (P = 0.31); $I^2 = 17\%$						
Test for overall effect: Z = 3.28 (P = 0.001)						
3.1.5 Sumatriptan						
Hämäläinen 1997b	5	23	2	23	0.5%	2.50 [0.54 , 11.60]
Rothner 1999b	9	62	3	30	0.7%	1.45 [0.42 , 4.98]
Rothner 1999c	11	66	5	36	1.1%	1.20 [0.45 , 3.18]
Callenbach 2007	12	46	9	46	1.8%	1.33 [0.62 , 2.86]
Rothner 1999a	43	208	10	35	2.9%	0.72 [0.40 , 1.30]
Fujita 2014	16	74	20	70	3.0%	0.76 [0.43 , 1.34]
Ahonen 2004	26	83	17	83	3.4%	1.53 [0.90 , 2.60]
Winner 1997	58	222	14	76	3.5%	1.42 [0.84 , 2.39]
Winner 2000	116	377	32	130	6.8%	1.25 [0.89 , 1.75]
Winner 2006	191	483	68	242	10.5%	1.41 [1.12 , 1.77]
Subtotal (95% CI)		**1644**		**771**	**34.3%**	**1.27 [1.10 , 1.48]**
Total events:	487		180			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 8.94$, df = 9 (P = 0.44); $I^2 = 0\%$						
Test for overall effect: Z = 3.15 (P = 0.002)						
3.1.6 Zolmitriptan						
Evers 2006	6	14	1	14	0.3%	6.00 [0.83 , 43.59]
Lewis 2007	58	148	24	127	5.1%	2.07 [1.37 , 3.13]
Rothner 2006	108	483	32	162	6.4%	1.13 [0.80 , 1.61]
NCT01211145	86	288	50	296	7.6%	1.77 [1.30 , 2.41]
Subtotal (95% CI)		**933**		**599**	**19.3%**	**1.66 [1.16 , 2.38]**



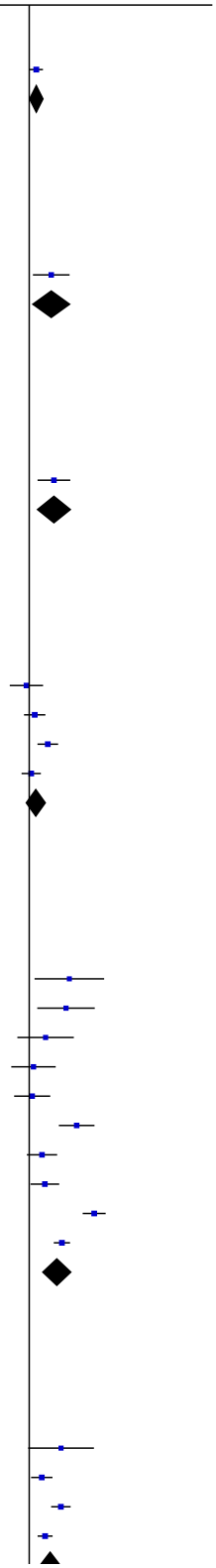
Analysis 3.1. (Continued)

NCT01211145	86	288	50	296	7.6%	1.77 [1.30 , 2.41]
Subtotal (95% CI)		**933**		**599**	**19.3%**	**1.66 [1.16 , 2.38]**
Total events:	258		107			
Heterogeneity: Tau² = 0.07; Chi² = 7.34, df = 3 (P = 0.06); I² = 59%						
Test for overall effect: Z = 2.79 (P = 0.005)						
Total (95% CI)		**4250**		**2511**	**100.0%**	**1.32 [1.19 , 1.47]**
Total events:	1300		577			
Heterogeneity: Tau² = 0.01; Chi² = 27.11, df = 20 (P = 0.13); I² = 26%						
Test for overall effect: Z = 5.11 (P < 0.00001)						
Test for subgroup differences: Chi² = 4.72, df = 5 (P = 0.45), I² = 0%						



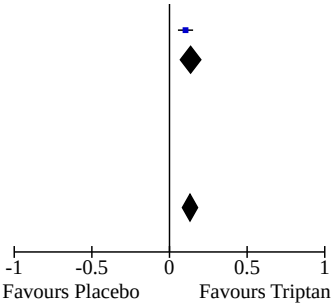
Analysis 3.2. Comparison 3: Triptans vs placebo in adolescents, Outcome 2: Adverse events (any)

Study or Subgroup	Triptan Events	Triptan Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
3.2.1 Almotriptan						
Linder 2008	57	548	10	172	5.9%	0.05 [0.00 , 0.09]
Subtotal (95% CI)		**548**		**172**	**5.9%**	**0.05 [0.00 , 0.09]**
Total events:	57		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.08 (P = 0.04)						
3.2.2 Eletriptan						
Winner 2007	55	129	32	113	4.5%	0.14 [0.02 , 0.26]
Subtotal (95% CI)		**129**		**113**	**4.5%**	**0.14 [0.02 , 0.26]**
Total events:	55		32			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.36 (P = 0.02)						
3.2.3 Naratriptan						
Rothner 1997	76	226	13	74	4.8%	0.16 [0.05 , 0.27]
Subtotal (95% CI)		**226**		**74**	**4.8%**	**0.16 [0.05 , 0.27]**
Total events:	76		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.96 (P = 0.003)						
3.2.4 Rizatriptan						
Winner 2002	50	149	52	147	4.7%	-0.02 [-0.13 , 0.09]
Visser 2004a	47	234	40	242	5.5%	0.04 [-0.03 , 0.11]
Ahonen 2006	16	116	2	116	5.6%	0.12 [0.05 , 0.19]
Ho 2012	81	337	83	365	5.6%	0.01 [-0.05 , 0.08]
Subtotal (95% CI)		**836**		**870**	**21.4%**	**0.04 [-0.02 , 0.10]**
Total events:	194		177			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 8.24$, df = 3 (P = 0.04); $I^2 = 64\%$						
Test for overall effect: Z = 1.36 (P = 0.17)						
3.2.5 Sumatriptan						
Hämäläinen 1997b	8	23	2	23	2.6%	0.26 [0.03 , 0.49]
Callenbach 2007	21	46	10	46	3.2%	0.24 [0.05 , 0.43]
Rothner 1999b	19	62	6	30	3.3%	0.11 [-0.08 , 0.29]
Rothner 1999c	11	66	5	36	4.0%	0.03 [-0.12 , 0.17]
Fujita 2014	12	74	10	70	4.6%	0.02 [-0.10 , 0.14]
Ahonen 2004	35	90	7	87	4.6%	0.31 [0.19 , 0.42]
Winner 2000	185	377	53	130	4.9%	0.08 [-0.02 , 0.18]
Rothner 1999a	129	445	16	85	5.1%	0.10 [0.01 , 0.19]
Winner 1997	239	289	102	252	5.4%	0.42 [0.35 , 0.50]
Winner 2006	145	493	20	245	5.8%	0.21 [0.16 , 0.27]
Subtotal (95% CI)		**1965**		**1004**	**43.5%**	**0.18 [0.09 , 0.27]**
Total events:	804		231			
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 63.26$, df = 9 (P < 0.00001); $I^2 = 86\%$						
Test for overall effect: Z = 3.88 (P = 0.0001)						
3.2.6 Zolmitriptan						
Evers 2006	10	29	4	29	2.8%	0.21 [-0.01 , 0.42]
Lewis 2007	37	200	19	184	5.5%	0.08 [0.01 , 0.15]
Rothner 2006	173	523	22	176	5.6%	0.21 [0.14 , 0.27]
NCT01211145	101	502	29	296	5.8%	0.10 [0.05 , 0.15]
Subtotal (95% CI)		**1254**		**685**	**19.8%**	**0.14 [0.07 , 0.20]**



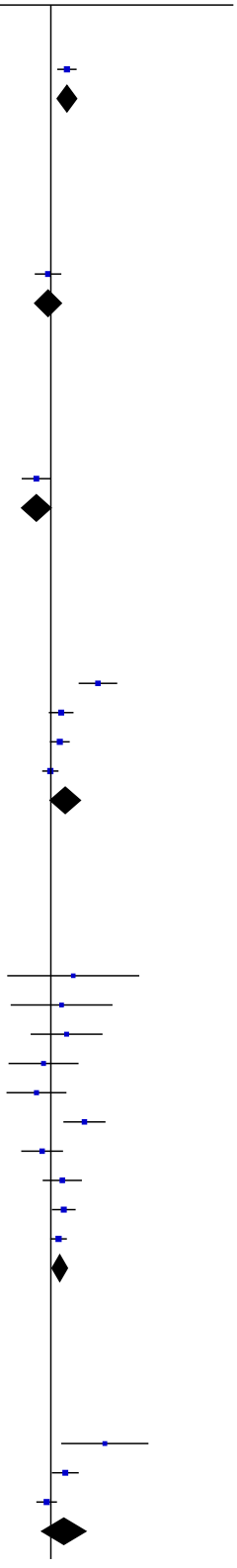
Analysis 3.2. (Continued)

NCT01211145	101	502	29	296	5.8%	0.10 [0.05 , 0.15]
Subtotal (95% CI)		**1254**		**685**	**19.8%**	**0.14 [0.07 , 0.20]**
Total events:	321		74			
Heterogeneity: Tau² = 0.00; Chi² = 9.07, df = 3 (P = 0.03); I² = 67%						
Test for overall effect: Z = 4.05 (P < 0.0001)						
Total (95% CI)		**4958**		**2918**	**100.0%**	**0.13 [0.08 , 0.18]**
Total events:	1507		537			
Heterogeneity: Tau² = 0.01; Chi² = 138.31, df = 20 (P < 0.00001); I² = 86%						
Test for overall effect: Z = 5.33 (P < 0.00001)						
Test for subgroup differences: Chi² = 14.26, df = 5 (P = 0.01), I² = 64.9%						



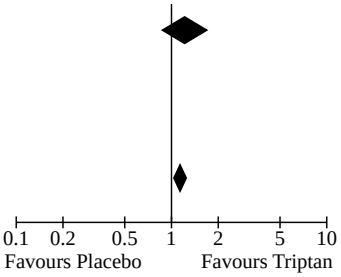
Analysis 3.3. Comparison 3: Triptans vs placebo in adolescents, Outcome 3: Headache relief

Study or Subgroup	Triptan Events	Triptan Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
3.3.1 Almotriptan						
Linder 2008	383	544	94	170	7.5%	1.27 [1.10 , 1.47]
Subtotal (95% CI)		**544**		**170**	**7.5%**	**1.27 [1.10 , 1.47]**
Total events:	383		94			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.25 (P = 0.001)						
3.3.2 Eletriptan						
Winner 2007	82	144	79	133	6.4%	0.96 [0.79 , 1.17]
Subtotal (95% CI)		**144**		**133**	**6.4%**	**0.96 [0.79 , 1.17]**
Total events:	82		79			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.41 (P = 0.68)						
3.3.3 Naratriptan						
Rothner 1997	113	226	46	74	6.0%	0.80 [0.65 , 1.00]
Subtotal (95% CI)		**226**		**74**	**6.0%**	**0.80 [0.65 , 1.00]**
Total events:	113		46			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.94 (P = 0.05)						
3.3.4 Rizatriptan						
Ahonen 2006	71	96	35	96	4.8%	2.03 [1.52 , 2.71]
Winner 2002	98	149	80	142	6.7%	1.17 [0.97 , 1.41]
Ho 2012	167	284	147	286	7.4%	1.14 [0.99 , 1.33]
Visser 2004a	159	233	165	240	7.9%	0.99 [0.88 , 1.12]
Subtotal (95% CI)		**762**		**764**	**26.9%**	**1.24 [0.99 , 1.56]**
Total events:	495		427			
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 20.70$, df = 3 (P = 0.0001); $I^2 = 86\%$						
Test for overall effect: Z = 1.87 (P = 0.06)						
3.3.5 Sumatriptan						
Hämäläinen 1997b	7	23	5	23	0.8%	1.40 [0.52 , 3.77]
Rothner 1999b	17	62	7	30	1.3%	1.18 [0.55 , 2.52]
Callenbach 2007	19	46	15	46	2.2%	1.27 [0.74 , 2.17]
Rothner 1999c	23	66	14	36	2.3%	0.90 [0.53 , 1.52]
Fujita 2014	23	74	27	70	2.9%	0.81 [0.51 , 1.26]
Ahonen 2004	53	83	32	83	4.4%	1.66 [1.21 , 2.27]
Rothner 1999a	96	186	20	34	4.5%	0.88 [0.64 , 1.20]
Winner 1997	111	222	32	76	4.7%	1.19 [0.88 , 1.59]
Winner 2000	243	377	69	130	6.9%	1.21 [1.02 , 1.45]
Winner 2006	316	483	141	242	7.9%	1.12 [0.99 , 1.27]
Subtotal (95% CI)		**1622**		**770**	**37.8%**	**1.14 [1.02 , 1.28]**
Total events:	908		362			
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 12.05$, df = 9 (P = 0.21); $I^2 = 25\%$						
Test for overall effect: Z = 2.28 (P = 0.02)						
3.3.6 Zolmitriptan						
Evers 2006	18	29	8	29	1.6%	2.25 [1.17 , 4.33]
Lewis 2007	97	148	67	127	6.4%	1.24 [1.02 , 1.52]
Rothner 2006	262	480	93	160	7.3%	0.94 [0.80 , 1.10]
Subtotal (95% CI)		**657**		**316**	**15.3%**	**1.21 [0.87 , 1.69]**
Total events:	377		168			

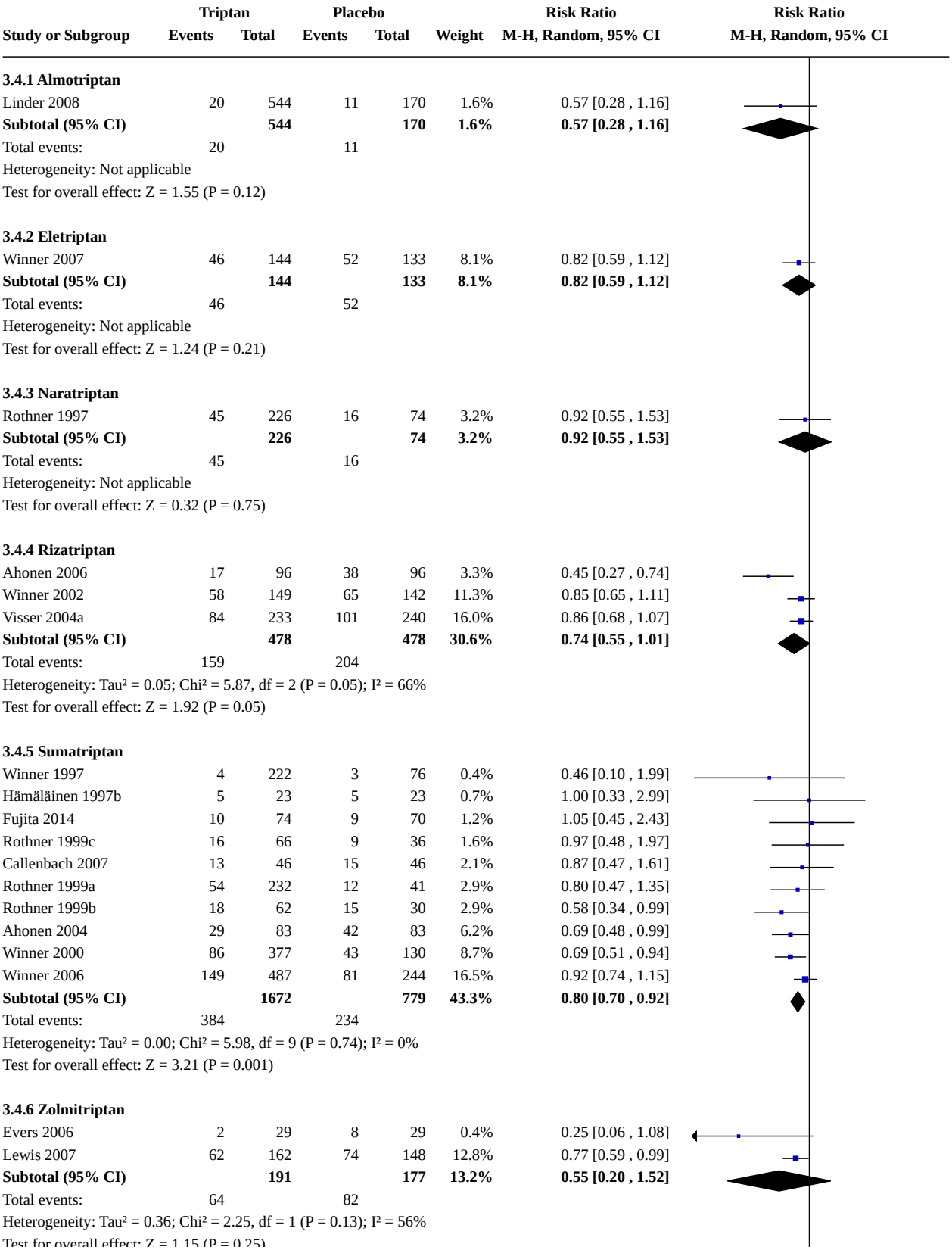


Analysis 3.3. (Continued)

Subtotal (95% CI)	**657**	**316**	**15.3%**	**1.21 [0.87 , 1.69]**	
Total events:	377	168			
Heterogeneity: Tau² = 0.06; Chi² = 9.85, df = 2 (P = 0.007); I² = 80%					
Test for overall effect: Z = 1.16 (P = 0.25)					
Total (95% CI)	**3955**	**2227**	**100.0%**	**1.14 [1.04 , 1.24]**	
Total events:	2358	1176			
Heterogeneity: Tau² = 0.02; Chi² = 57.11, df = 19 (P < 0.0001); I² = 67%					
Test for overall effect: Z = 2.70 (P = 0.007)					
Test for subgroup differences: Chi² = 15.11, df = 5 (P = 0.010), I² = 66.9%					



Analysis 3.4. Comparison 3: Triptans vs placebo in adolescents, Outcome 4: Rescue medication

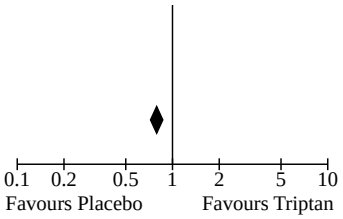


Analysis 3.4. (Continued)

Heterogeneity: Tau² = 0.36; Chi² = 2.25, df = 1 (P = 0.13); I² = 56%
Test for overall effect: Z = 1.15 (P = 0.25)

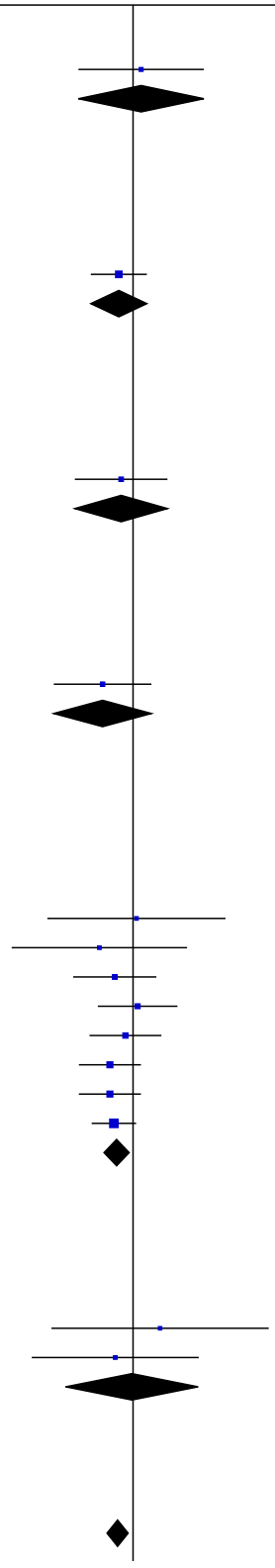
Total (95% CI)	**3255**	**1811**	**100.0%**	**0.79 [0.72 , 0.87]**	
Total events:	718	599			

Heterogeneity: Tau² = 0.00; Chi² = 15.47, df = 17 (P = 0.56); I² = 0%
Test for overall effect: Z = 5.08 (P < 0.00001)
Test for subgroup differences: Chi² = 1.88, df = 5 (P = 0.87), I² = 0%



Analysis 3.5. Comparison 3: Triptans vs placebo in adolescents, Outcome 5: Headache recurrence

Study or Subgroup	Triptan Events	Triptan Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
3.5.1 Almotriptan						
Linder 2008	23	383	5	94	2.8%	1.13 [0.44 , 2.89]
Subtotal (95% CI)		**383**		**94**	**2.8%**	**1.13 [0.44 , 2.89]**
Total events:	23		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.25 (P = 0.80)						
3.5.2 Eletriptan						
Winner 2007	26	82	31	79	14.2%	0.81 [0.53 , 1.23]
Subtotal (95% CI)		**82**		**79**	**14.2%**	**0.81 [0.53 , 1.23]**
Total events:	26		31			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.00 (P = 0.32)						
3.5.3 Naratriptan						
Rothner 1997	24	153	9	48	5.2%	0.84 [0.42 , 1.67]
Subtotal (95% CI)		**153**		**48**	**5.2%**	**0.84 [0.42 , 1.67]**
Total events:	24		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.50 (P = 0.61)						
3.5.4 Rizatriptan						
Winner 2002	11	98	14	79	4.7%	0.63 [0.30 , 1.32]
Subtotal (95% CI)		**98**		**79**	**4.7%**	**0.63 [0.30 , 1.32]**
Total events:	11		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.22 (P = 0.22)						
3.5.5 Sumatriptan						
Hämäläinen 1997b	0	7	0	5		Not estimable
Callenbach 2007	4	19	3	15	1.4%	1.05 [0.28 , 4.00]
Ahonen 2004	4	53	4	32	1.4%	0.60 [0.16 , 2.25]
Winner 1997	31	163	10	40	6.4%	0.76 [0.41 , 1.42]
Rothner 1999c	20	56	11	33	7.0%	1.07 [0.59 , 1.95]
Winner 2000	44	243	14	69	8.6%	0.89 [0.52 , 1.53]
Rothner 1999b	23	61	16	30	11.6%	0.71 [0.44 , 1.13]
Rothner 1999a	23	61	16	30	11.6%	0.71 [0.44 , 1.13]
Winner 2006	65	275	40	127	22.5%	0.75 [0.54 , 1.05]
Subtotal (95% CI)		**938**		**381**	**70.6%**	**0.78 [0.65 , 0.94]**
Total events:	214		114			
Heterogeneity: Tau² = 0.00; Chi² = 2.08, df = 7 (P = 0.96); I² = 0%						
Test for overall effect: Z = 2.57 (P = 0.01)						
3.5.6 Zolmitriptan						
Evers 2006	3	14	2	14	0.9%	1.50 [0.29 , 7.65]
NCT01211145	5	62	4	38	1.6%	0.77 [0.22 , 2.68]
Subtotal (95% CI)		**76**		**52**	**2.5%**	**0.98 [0.36 , 2.65]**
Total events:	8		6			
Heterogeneity: Tau² = 0.00; Chi² = 0.41, df = 1 (P = 0.52); I² = 0%						
Test for overall effect: Z = 0.03 (P = 0.97)						
Total (95% CI)		**1730**		**733**	**100.0%**	**0.79 [0.68 , 0.93]**
Total events:	306		179			



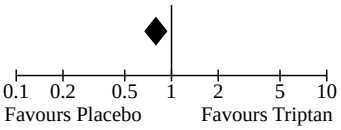
Analysis 3.5. (Continued)

Total (95% CI)	**1730**	**733**	**100.0%**	**0.79 [0.68 , 0.93]**	
Total events:	306	179			

Heterogeneity: Tau² = 0.00; Chi² = 3.63, df = 13 (P = 0.99); I² = 0%

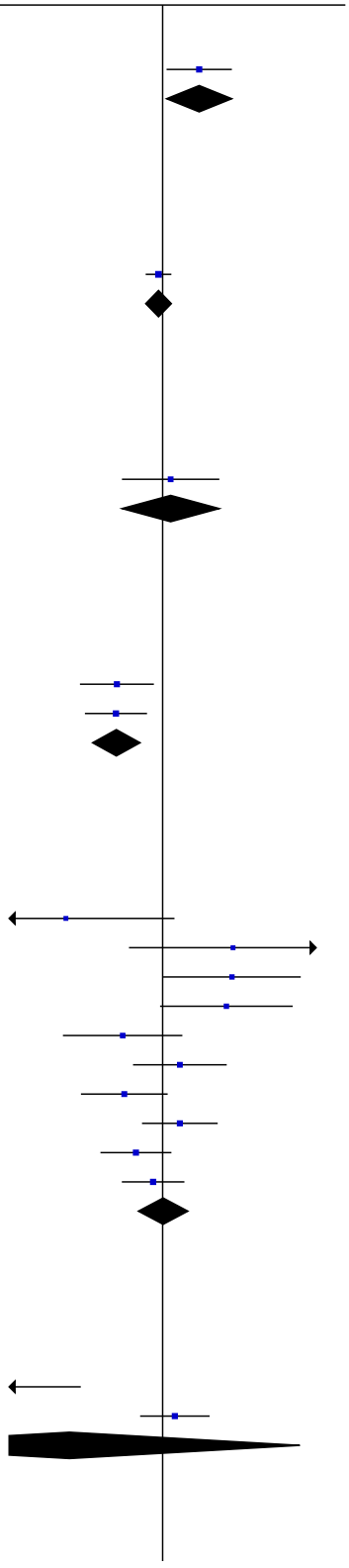
Test for overall effect: Z = 2.87 (P = 0.004)

Test for subgroup differences: Chi² = 1.14, df = 5 (P = 0.95), I² = 0%



Analysis 3.6. Comparison 3: Triptans vs placebo in adolescents, Outcome 6: Presence of nausea

Study or Subgroup	Triptan Events	Triptan Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
3.6.1 Almotriptan						
Linder 2008	65	186	41	170	7.8%	1.45 [1.04 , 2.02]
Subtotal (95% CI)		**186**		**170**	**7.8%**	**1.45 [1.04 , 2.02]**
Total events:	65		41			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.20 (P = 0.03)						
3.6.2 Eletriptan						
Winner 2007	108	144	104	133	10.0%	0.96 [0.84 , 1.09]
Subtotal (95% CI)		**144**		**133**	**10.0%**	**0.96 [0.84 , 1.09]**
Total events:	108		104			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.63 (P = 0.53)						
3.6.3 Naratriptan						
Rothner 1997	53	226	16	74	5.8%	1.08 [0.66 , 1.78]
Subtotal (95% CI)		**226**		**74**	**5.8%**	**1.08 [0.66 , 1.78]**
Total events:	53		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.32 (P = 0.75)						
3.6.4 Rizatriptan						
Winner 2002	33	149	50	142	7.2%	0.63 [0.43 , 0.91]
Ho 2012	52	381	85	388	8.0%	0.62 [0.45 , 0.85]
Subtotal (95% CI)		**530**		**530**	**15.2%**	**0.63 [0.49 , 0.80]**
Total events:	85		135			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.97); I² = 0%						
Test for overall effect: Z = 3.82 (P = 0.0001)						
3.6.5 Sumatriptan						
Ueberall 1999	3	14	8	14	2.1%	0.38 [0.12 , 1.13]
Fujita 2014	7	18	4	21	2.2%	2.04 [0.71 , 5.86]
Rothner 1999a	80	232	7	41	4.0%	2.02 [1.01 , 4.06]
Rothner 1999c	28	66	8	36	4.2%	1.91 [0.97 , 3.74]
Callenbach 2007	12	46	18	46	4.8%	0.67 [0.36 , 1.22]
Rothner 1999b	32	62	13	30	6.0%	1.19 [0.74 , 1.92]
Hämäläinen 2002	20	59	29	58	6.4%	0.68 [0.44 , 1.05]
Winner 1997	80	222	23	76	7.1%	1.19 [0.81 , 1.75]
Winner 2000	73	377	33	130	7.4%	0.76 [0.53 , 1.09]
Winner 2006	87	487	48	244	7.9%	0.91 [0.66 , 1.25]
Subtotal (95% CI)		**1583**		**696**	**52.2%**	**1.01 [0.78 , 1.29]**
Total events:	422		191			
Heterogeneity: Tau² = 0.08; Chi² = 20.73, df = 9 (P = 0.01); I² = 57%						
Test for overall effect: Z = 0.04 (P = 0.97)						
3.6.6 Zolmitriptan						
Evers 2006	2	29	18	29	1.5%	0.11 [0.03 , 0.44]
Rothner 2006	108	483	32	162	7.5%	1.13 [0.80 , 1.61]
Subtotal (95% CI)		**512**		**191**	**9.0%**	**0.39 [0.04 , 4.02]**
Total events:	110		50			
Heterogeneity: Tau² = 2.60; Chi² = 11.02, df = 1 (P = 0.0009); I² = 91%						
Test for overall effect: Z = 0.79 (P = 0.43)						



Analysis 3.6. (Continued)

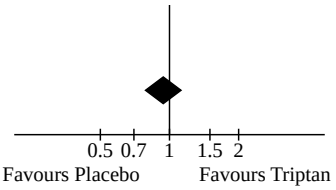
Test for overall effect: Z = 0.79 (P = 0.43)

Total (95% CI)	**3181**	**1794**	**100.0%**	**0.94 [0.79 , 1.12]**	
Total events:	843	537			

Heterogeneity: Tau² = 0.08; Chi² = 49.30, df = 16 (P < 0.0001); I² = 68%

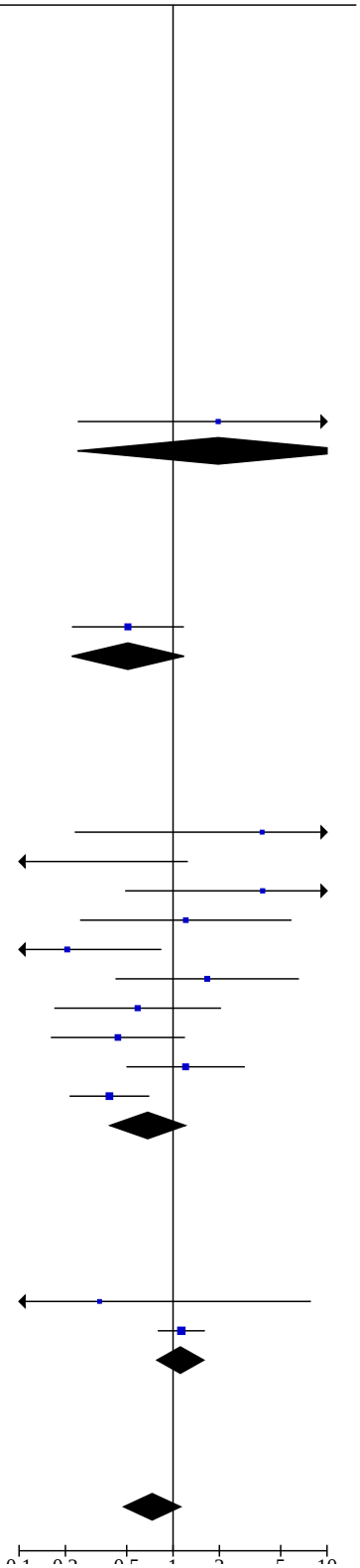
Test for overall effect: Z = 0.69 (P = 0.49)

Test for subgroup differences: Chi² = 18.77, df = 5 (P = 0.002), I² = 73.4%



Analysis 3.7. Comparison 3: Triptans vs placebo in adolescents, Outcome 7: Presence of vomiting

Study or Subgroup	Triptan Events	Triptan Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
3.7.1 Almotriptan						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.7.2 Eletriptan						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.7.3 Naratriptan						
Rothner 1997	6	226	1	74	3.4%	1.96 [0.24 , 16.05]
Subtotal (95% CI)		**226**		**74**	**3.4%**	**1.96 [0.24 , 16.05]**
Total events:	6		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.63 (P = 0.53)						
3.7.4 Rizatriptan						
Ho 2012	8	381	16	388	11.1%	0.51 [0.22 , 1.18]
Subtotal (95% CI)		**381**		**388**	**11.1%**	**0.51 [0.22 , 1.18]**
Total events:	8		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.58 (P = 0.11)						
3.7.5 Sumatriptan						
Winner 2000	4	18	0	7	2.1%	3.79 [0.23 , 62.47]
Ueberall 1999	0	14	6	14	2.1%	0.08 [0.00 , 1.25]
Rothner 1999c	7	66	1	36	3.5%	3.82 [0.49 , 29.82]
Rothner 1999b	5	62	2	30	5.3%	1.21 [0.25 , 5.88]
Winner 1997	3	222	5	76	6.2%	0.21 [0.05 , 0.84]
Rothner 1999c	5	46	3	46	6.4%	1.67 [0.42 , 6.57]
Rothner 1999a	10	232	3	41	7.3%	0.59 [0.17 , 2.05]
Winner 2006	7	487	8	244	9.3%	0.44 [0.16 , 1.19]
Winner 2000	21	377	6	130	10.5%	1.21 [0.50 , 2.92]
Hämäläinen 2002	11	59	28	58	14.0%	0.39 [0.21 , 0.70]
Subtotal (95% CI)		**1583**		**682**	**66.8%**	**0.68 [0.39 , 1.20]**
Total events:	73		62			
Heterogeneity: Tau² = 0.34; Chi² = 16.93, df = 9 (P = 0.05); I² = 47%						
Test for overall effect: Z = 1.32 (P = 0.19)						
3.7.6 Zolmitriptan						
Evers 2006	0	29	1	29	1.7%	0.33 [0.01 , 7.86]
Rothner 2006	108	483	32	162	17.1%	1.13 [0.80 , 1.61]
Subtotal (95% CI)		**512**		**191**	**18.8%**	**1.12 [0.79 , 1.58]**
Total events:	108		33			
Heterogeneity: Tau² = 0.00; Chi² = 0.57, df = 1 (P = 0.45); I² = 0%						
Test for overall effect: Z = 0.61 (P = 0.54)						
Total (95% CI)		**2702**		**1335**	**100.0%**	**0.73 [0.48 , 1.12]**
Total events:	195		112			
Heterogeneity: Tau² = 0.24; Chi² = 25.10, df = 13 (P = 0.02); I² = 48%						



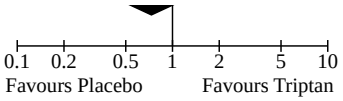
Analysis 3.7. (Continued)

Total events: 195 112

Heterogeneity: Tau² = 0.24; Chi² = 25.10, df = 13 (P = 0.02); I² = 48%

Test for overall effect: Z = 1.44 (P = 0.15)

Test for subgroup differences: Chi² = 4.64, df = 3 (P = 0.20), I² = 35.4%

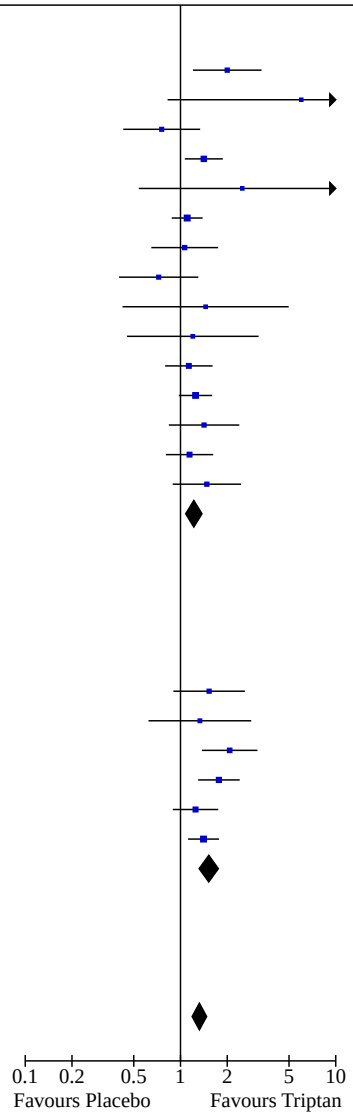


Comparison 4. Triptans vs placebo in adolescents, subgroup analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Pain-free by route (oral or intranasal)	21	6764	Risk Ratio (M-H, Random, 95% CI)	1.32 [1.19, 1.47]
4.1.1 Oral	15	4415	Risk Ratio (M-H, Random, 95% CI)	1.22 [1.08, 1.38]
4.1.2 Intranasal	6	2349	Risk Ratio (M-H, Random, 95% CI)	1.52 [1.32, 1.75]
4.2 Sumatriptan vs placebo by route (oral or intranasal)	10	2415	Risk Ratio (M-H, Random, 95% CI)	1.27 [1.10, 1.48]
4.2.1 Intranasal	4	1490	Risk Ratio (M-H, Random, 95% CI)	1.37 [1.15, 1.63]
4.2.2 Oral	6	925	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.75, 1.43]
4.3 Zolmitriptan vs placebo by route (oral or intranasal)	4	1532	Risk Ratio (M-H, Random, 95% CI)	1.66 [1.16, 2.38]
4.3.1 Intranasal	2	859	Risk Ratio (M-H, Random, 95% CI)	1.87 [1.46, 2.40]
4.3.2 Oral	2	673	Risk Ratio (M-H, Random, 95% CI)	1.94 [0.42, 9.07]
4.4 Pain-free by preventive medication	21	6764	Risk Ratio (M-H, Random, 95% CI)	1.32 [1.19, 1.47]
4.4.1 Preventive medication not permitted	8	1658	Risk Ratio (M-H, Random, 95% CI)	1.39 [1.14, 1.69]
4.4.2 Preventive medication permitted	8	2316	Risk Ratio (M-H, Random, 95% CI)	1.28 [1.04, 1.56]
4.4.3 Unsure	5	2790	Risk Ratio (M-H, Random, 95% CI)	1.33 [1.11, 1.61]

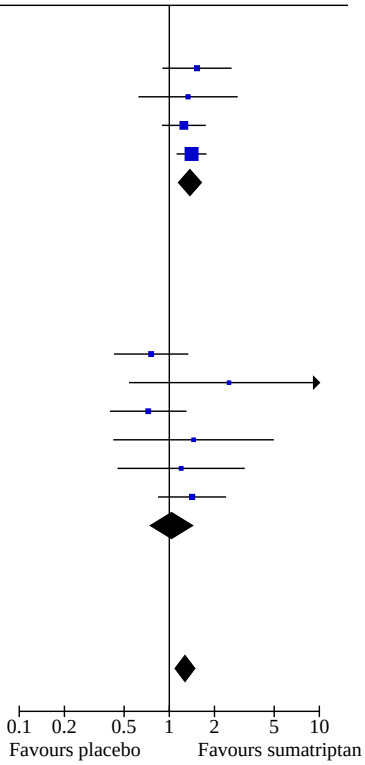
Analysis 4.1. Comparison 4: Triptans vs placebo in adolescents, subgroup analysis, Outcome 1: Pain-free by route (oral or intranasal)

Study or Subgroup	Triptan Events	Triptan Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
4.1.1 Oral						
Ahonen 2006	34	96	17	96	3.7%	2.00 [1.20 , 3.33]
Evers 2006	6	14	1	14	0.3%	6.00 [0.83 , 43.59]
Fujita 2014	16	74	20	70	3.0%	0.76 [0.43 , 1.34]
Ho 2012	87	284	62	286	8.5%	1.41 [1.07 , 1.87]
Hämäläinen 1997b	5	23	2	23	0.5%	2.50 [0.54 , 11.60]
Linder 2008	212	544	60	170	10.6%	1.10 [0.88 , 1.39]
Rothner 1997	52	226	16	74	3.8%	1.06 [0.65 , 1.75]
Rothner 1999a	43	208	10	35	2.9%	0.72 [0.40 , 1.30]
Rothner 1999b	9	62	3	30	0.7%	1.45 [0.42 , 4.98]
Rothner 1999c	11	66	5	36	1.1%	1.20 [0.45 , 3.18]
Rothner 2006	108	483	32	162	6.4%	1.13 [0.80 , 1.61]
Visser 2004a	91	233	75	240	9.8%	1.25 [0.98 , 1.60]
Winner 1997	58	222	14	76	3.5%	1.42 [0.84 , 2.39]
Winner 2002	48	149	40	142	6.4%	1.14 [0.81 , 1.62]
Winner 2007	32	144	20	133	3.7%	1.48 [0.89 , 2.45]
Subtotal (95% CI)		**2828**		**1587**	**64.8%**	**1.22 [1.08 , 1.38]**
Total events:	812		377			
Heterogeneity: Tau² = 0.01; Chi² = 16.08, df = 14 (P = 0.31); I² = 13%						
Test for overall effect: Z = 3.21 (P = 0.001)						
4.1.2 Intranasal						
Ahonen 2004	26	83	17	83	3.4%	1.53 [0.90 , 2.60]
Callenbach 2007	12	46	9	46	1.8%	1.33 [0.62 , 2.86]
Lewis 2007	58	148	24	127	5.1%	2.07 [1.37 , 3.13]
NCT01211145	86	288	50	296	7.6%	1.77 [1.30 , 2.41]
Winner 2000	116	377	32	130	6.8%	1.25 [0.89 , 1.75]
Winner 2006	191	483	68	242	10.5%	1.41 [1.12 , 1.77]
Subtotal (95% CI)		**1425**		**924**	**35.2%**	**1.52 [1.32 , 1.75]**
Total events:	489		200			
Heterogeneity: Tau² = 0.00; Chi² = 4.95, df = 5 (P = 0.42); I² = 0%						
Test for overall effect: Z = 5.78 (P < 0.00001)						
Total (95% CI)		**4253**		**2511**	**100.0%**	**1.32 [1.19 , 1.47]**
Total events:	1301		577			
Heterogeneity: Tau² = 0.01; Chi² = 27.15, df = 20 (P = 0.13); I² = 26%						
Test for overall effect: Z = 5.12 (P < 0.00001)						
Test for subgroup differences: Chi² = 5.41, df = 1 (P = 0.02), I² = 81.5%						



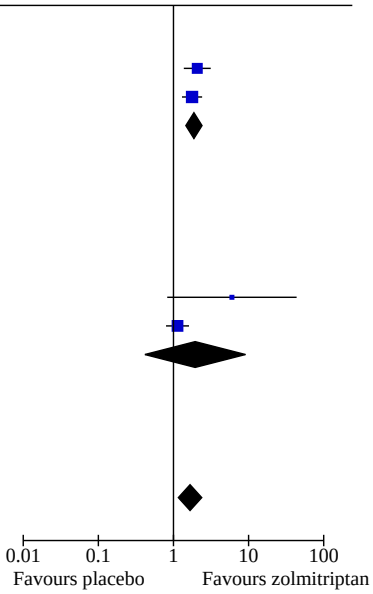
Analysis 4.2. Comparison 4: Triptans vs placebo in adolescents, subgroup analysis, Outcome 2: Sumatriptan vs placebo by route (oral or intranasal)

Study or Subgroup	Sumatriptan Events	Sumatriptan Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
4.2.1 Intranasal						
Ahonen 2004	26	83	17	83	7.9%	1.53 [0.90 , 2.60]
Callenbach 2007	12	46	9	46	3.8%	1.33 [0.62 , 2.86]
Winner 2000	116	377	32	130	19.7%	1.25 [0.89 , 1.75]
Winner 2006	191	483	68	242	42.3%	1.41 [1.12 , 1.77]
Subtotal (95% CI)		**989**		**501**	**73.7%**	**1.37 [1.15 , 1.63]**
Total events:	345		126			
Heterogeneity: Tau² = 0.00; Chi² = 0.51, df = 3 (P = 0.92); I² = 0%						
Test for overall effect: Z = 3.56 (P = 0.0004)						
4.2.2 Oral						
Fujita 2014	16	74	20	70	6.9%	0.76 [0.43 , 1.34]
Hämäläinen 1997b	5	23	2	23	0.9%	2.50 [0.54 , 11.60]
Rothner 1999a	43	208	10	35	6.5%	0.72 [0.40 , 1.30]
Rothner 1999b	9	62	3	30	1.5%	1.45 [0.42 , 4.98]
Rothner 1999c	11	66	5	36	2.3%	1.20 [0.45 , 3.18]
Winner 1997	58	222	14	76	8.2%	1.42 [0.84 , 2.39]
Subtotal (95% CI)		**655**		**270**	**26.3%**	**1.03 [0.75 , 1.43]**
Total events:	142		54			
Heterogeneity: Tau² = 0.02; Chi² = 5.71, df = 5 (P = 0.34); I² = 12%						
Test for overall effect: Z = 0.21 (P = 0.84)						
Total (95% CI)		**1644**		**771**	**100.0%**	**1.27 [1.10 , 1.48]**
Total events:	487		180			
Heterogeneity: Tau² = 0.00; Chi² = 8.94, df = 9 (P = 0.44); I² = 0%						
Test for overall effect: Z = 3.15 (P = 0.002)						
Test for subgroup differences: Chi² = 2.29, df = 1 (P = 0.13), I² = 56.4%						



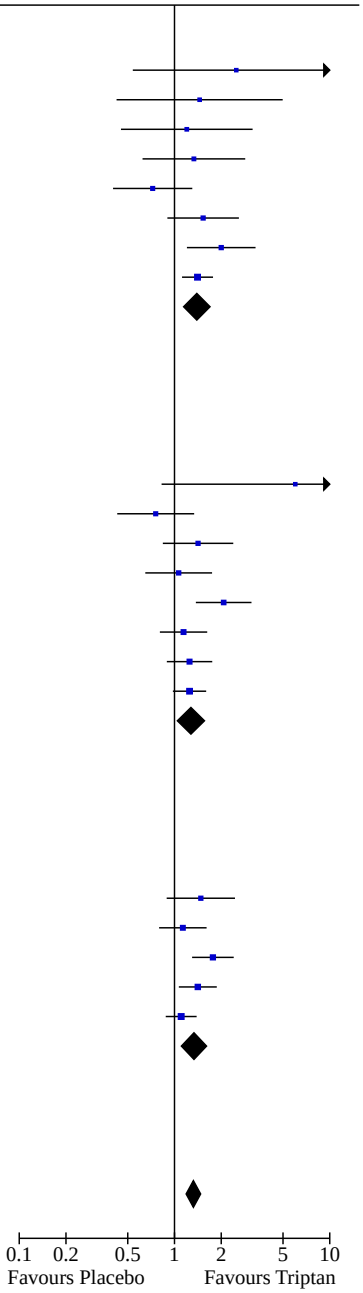
Analysis 4.3. Comparison 4: Triptans vs placebo in adolescents, subgroup analysis, Outcome 3: Zolmitriptan vs placebo by route (oral or intranasal)

Study or Subgroup	Zolmitriptan Events	Zolmitriptan Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
4.3.1 Intranasal						
Lewis 2007	58	148	24	127	29.2%	2.07 [1.37 , 3.13]
NCT01211145	86	288	50	296	35.2%	1.77 [1.30 , 2.41]
Subtotal (95% CI)		**436**		**423**	**64.4%**	**1.87 [1.46 , 2.40]**
Total events:	144		74			
Heterogeneity: Tau² = 0.00; Chi² = 0.37, df = 1 (P = 0.54); I² = 0%						
Test for overall effect: Z = 4.97 (P < 0.00001)						
4.3.2 Oral						
Evers 2006	6	14	1	14	3.0%	6.00 [0.83 , 43.59]
Rothner 2006	108	483	32	162	32.6%	1.13 [0.80 , 1.61]
Subtotal (95% CI)		**497**		**176**	**35.6%**	**1.94 [0.42 , 9.07]**
Total events:	114		33			
Heterogeneity: Tau² = 0.88; Chi² = 2.67, df = 1 (P = 0.10); I² = 63%						
Test for overall effect: Z = 0.85 (P = 0.40)						
Total (95% CI)		**933**		**599**	**100.0%**	**1.66 [1.16 , 2.38]**
Total events:	258		107			
Heterogeneity: Tau² = 0.07; Chi² = 7.34, df = 3 (P = 0.06); I² = 59%						
Test for overall effect: Z = 2.79 (P = 0.005)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.96), I² = 0%						



Analysis 4.4. Comparison 4: Triptans vs placebo in adolescents, subgroup analysis, Outcome 4: Pain-free by preventive medication

Study or Subgroup	Triptan Events	Triptan Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
4.4.1 Preventive medication not permitted						
Hämäläinen 1997b	5	23	2	23	0.5%	2.50 [0.54 , 11.60]
Rothner 1999b	9	62	3	30	0.7%	1.45 [0.42 , 4.98]
Rothner 1999c	11	66	5	36	1.1%	1.20 [0.45 , 3.18]
Callenbach 2007	12	46	9	46	1.8%	1.33 [0.62 , 2.86]
Rothner 1999a	43	208	10	35	2.9%	0.72 [0.40 , 1.30]
Ahonen 2004	26	83	17	83	3.4%	1.53 [0.90 , 2.60]
Ahonen 2006	34	96	17	96	3.7%	2.00 [1.20 , 3.33]
Winner 2006	191	483	68	242	10.5%	1.41 [1.12 , 1.77]
Subtotal (95% CI)		**1067**		**591**	**24.6%**	**1.39 [1.14 , 1.69]**
Total events:	331		131			
Heterogeneity: Tau² = 0.01; Chi² = 7.52, df = 7 (P = 0.38); I² = 7%						
Test for overall effect: Z = 3.32 (P = 0.0009)						
4.4.2 Preventive medication permitted						
Evers 2006	6	14	1	14	0.3%	6.00 [0.83 , 43.59]
Fujita 2014	16	74	20	70	3.0%	0.76 [0.43 , 1.34]
Winner 1997	58	222	14	76	3.5%	1.42 [0.84 , 2.39]
Rothner 1997	52	226	16	74	3.8%	1.06 [0.65 , 1.75]
Lewis 2007	58	148	24	127	5.1%	2.07 [1.37 , 3.13]
Winner 2002	48	149	40	142	6.4%	1.14 [0.81 , 1.62]
Winner 2000	116	377	32	130	6.8%	1.25 [0.89 , 1.75]
Visser 2004a	91	233	75	240	9.8%	1.25 [0.98 , 1.60]
Subtotal (95% CI)		**1443**		**873**	**38.7%**	**1.28 [1.04 , 1.56]**
Total events:	445		222			
Heterogeneity: Tau² = 0.03; Chi² = 12.02, df = 7 (P = 0.10); I² = 42%						
Test for overall effect: Z = 2.38 (P = 0.02)						
4.4.3 Unsure						
Winner 2007	32	144	20	133	3.7%	1.48 [0.89 , 2.45]
Rothner 2006	108	483	32	162	6.4%	1.13 [0.80 , 1.61]
NCT01211145	86	288	50	296	7.6%	1.77 [1.30 , 2.41]
Ho 2012	87	284	62	286	8.5%	1.41 [1.07 , 1.87]
Linder 2008	212	544	60	170	10.6%	1.10 [0.88 , 1.39]
Subtotal (95% CI)		**1743**		**1047**	**36.7%**	**1.33 [1.11 , 1.61]**
Total events:	525		224			
Heterogeneity: Tau² = 0.02; Chi² = 6.95, df = 4 (P = 0.14); I² = 42%						
Test for overall effect: Z = 3.04 (P = 0.002)						
Total (95% CI)		**4253**		**2511**	**100.0%**	**1.32 [1.19 , 1.47]**
Total events:	1301		577			
Heterogeneity: Tau² = 0.01; Chi² = 27.15, df = 20 (P = 0.13); I² = 26%						
Test for overall effect: Z = 5.12 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.37, df = 2 (P = 0.83), I² = 0%						



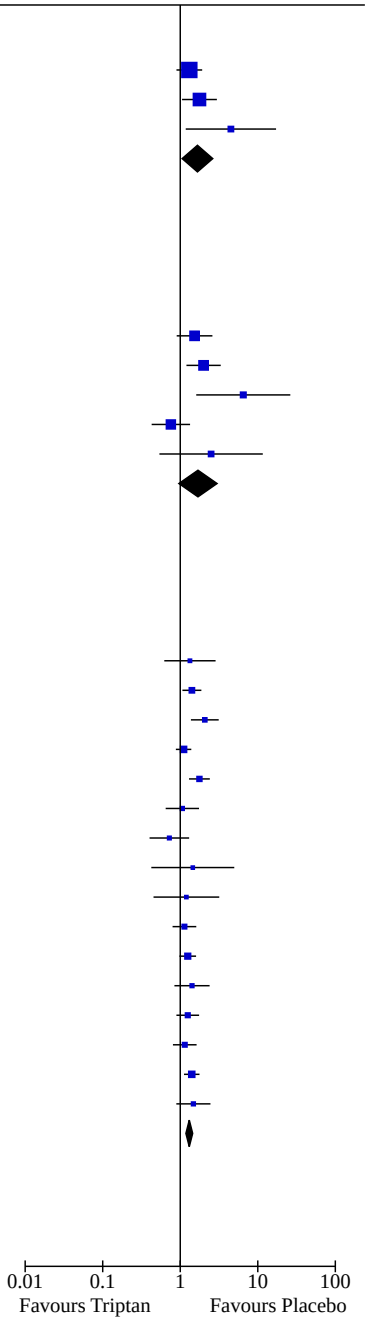
Comparison 5. Triptans vs placebo by age, subgroup analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Age group	23		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1.1 Children	3	345	Risk Ratio (M-H, Random, 95% CI)	1.67 [1.06, 2.62]
5.1.2 Mixed children and adolescents	5	606	Risk Ratio (M-H, Random, 95% CI)	1.69 [0.96, 2.98]
5.1.3 Adolescent	16	6188	Risk Ratio (M-H, Random, 95% CI)	1.31 [1.18, 1.45]

Analysis 5.1. Comparison 5: Triptans vs placebo by age, subgroup analysis, Outcome 1: Age group

Study or Subgroup	Triptan Events	Triptan Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
5.1.1 Children						
Ho 2012	39	98	31	102	50.9%	1.31 [0.89 , 1.92]
Hämäläinen 2002	27	59	15	58	39.1%	1.77 [1.06 , 2.97]
Ueberall 1999	9	14	2	14	10.0%	4.50 [1.18 , 17.21]
Subtotal (95% CI)		**171**		**174**	**100.0%**	**1.67 [1.06 , 2.62]**
Total events:	75		48			
Heterogeneity: Tau² = 0.07; Chi² = 3.47, df = 2 (P = 0.18); I² = 42%						
Test for overall effect: Z = 2.21 (P = 0.03)						
5.1.2 Mixed children and adolescents						
Ahonen 2004	26	83	17	83	26.5%	1.53 [0.90 , 2.60]
Ahonen 2006	34	96	17	96	27.0%	2.00 [1.20 , 3.33]
Evers 2006	13	29	2	29	11.1%	6.50 [1.61 , 26.28]
Fujita 2014	16	74	20	70	25.6%	0.76 [0.43 , 1.34]
Hämäläinen 1997b	5	23	2	23	9.8%	2.50 [0.54 , 11.60]
Subtotal (95% CI)		**305**		**301**	**100.0%**	**1.69 [0.96 , 2.98]**
Total events:	94		58			
Heterogeneity: Tau² = 0.24; Chi² = 11.57, df = 4 (P = 0.02); I² = 65%						
Test for overall effect: Z = 1.82 (P = 0.07)						
5.1.3 Adolescent						
Callenbach 2007	12	46	9	46	1.7%	1.33 [0.62 , 2.86]
Ho 2012	87	284	62	286	9.8%	1.41 [1.07 , 1.87]
Lewis 2007	58	148	24	127	5.2%	2.07 [1.37 , 3.13]
Linder 2008	212	544	60	170	13.3%	1.10 [0.88 , 1.39]
NCT01211145	86	288	50	296	8.5%	1.77 [1.30 , 2.41]
Rothner 1997	52	226	16	74	3.8%	1.06 [0.65 , 1.75]
Rothner 1999a	43	208	10	35	2.7%	0.72 [0.40 , 1.30]
Rothner 1999b	9	62	3	30	0.7%	1.45 [0.42 , 4.98]
Rothner 1999c	11	66	5	36	1.0%	1.20 [0.45 , 3.18]
Rothner 2006	108	483	32	162	6.8%	1.13 [0.80 , 1.61]
Visser 2004a	91	233	75	240	12.0%	1.25 [0.98 , 1.60]
Winner 1997	58	222	14	76	3.4%	1.42 [0.84 , 2.39]
Winner 2000	116	377	32	130	7.4%	1.25 [0.89 , 1.75]
Winner 2002	48	149	40	142	6.9%	1.14 [0.81 , 1.62]
Winner 2006	191	483	68	242	13.3%	1.41 [1.12 , 1.77]
Winner 2007	32	144	20	133	3.6%	1.48 [0.89 , 2.45]
Subtotal (95% CI)		**3963**		**2225**	**100.0%**	**1.31 [1.18 , 1.45]**
Total events:	1214		520			
Heterogeneity: Tau² = 0.01; Chi² = 17.64, df = 15 (P = 0.28); I² = 15%						
Test for overall effect: Z = 5.24 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.76, df = 2 (P = 0.42), I² = 0%						



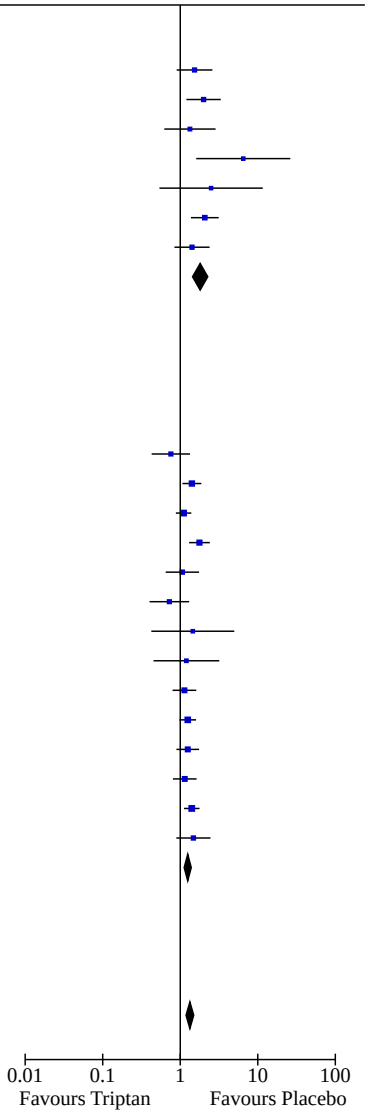
Comparison 6. Triptans vs placebo in adolescents, sensitivity analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Study design	21	6794	Risk Ratio (M-H, Random, 95% CI)	1.33 [1.19, 1.49]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1.1 Cross-over	7	1127	Risk Ratio (M-H, Random, 95% CI)	1.81 [1.44, 2.26]
6.1.2 Parallel	14	5667	Risk Ratio (M-H, Random, 95% CI)	1.25 [1.12, 1.39]
6.2 Allocation concealment	21		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.2.1 Low	8	2365	Risk Ratio (M-H, Random, 95% CI)	1.50 [1.19, 1.89]
6.2.2 Unclear	13	4429	Risk Ratio (M-H, Random, 95% CI)	1.25 [1.12, 1.40]
6.3 Source of funding	21		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.3.1 Pharmaceutical	17	6332	Risk Ratio (M-H, Random, 95% CI)	1.29 [1.16, 1.43]
6.3.2 Non-pharmaceutical	2	104	Risk Ratio (M-H, Random, 95% CI)	4.22 [1.50, 11.84]
6.3.3 Unclear	2	358	Risk Ratio (M-H, Random, 95% CI)	1.76 [1.22, 2.54]
6.4 Reported in a journal	21		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.4.1 Journal report	15	5175	Risk Ratio (M-H, Random, 95% CI)	1.34 [1.18, 1.52]
6.4.2 Registry or abstract only	6	1619	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.94, 1.71]
6.5 Sample size	21	6794	Risk Ratio (M-H, Random, 95% CI)	1.33 [1.19, 1.49]
6.5.1 Sample size ≤ 50	2	104	Risk Ratio (M-H, Random, 95% CI)	4.22 [1.50, 11.84]
6.5.2 Sample size > 50	19	6690	Risk Ratio (M-H, Random, 95% CI)	1.31 [1.18, 1.46]

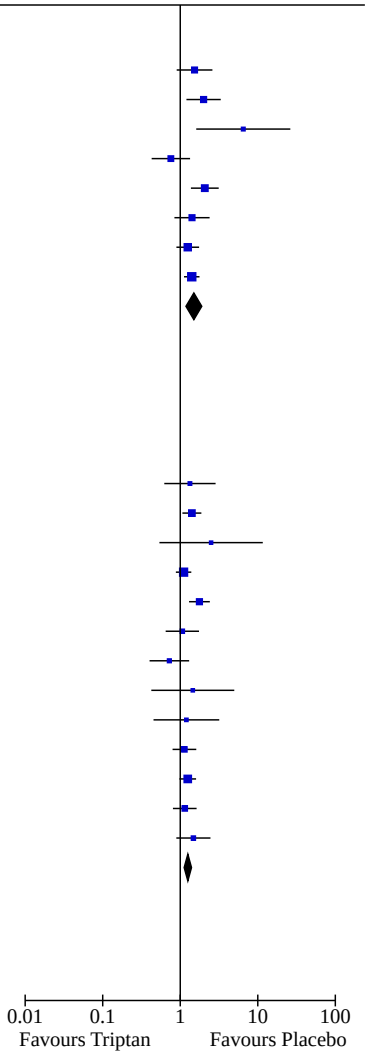
Analysis 6.1. Comparison 6: Triptans vs placebo in adolescents, sensitivity analysis, Outcome 1: Study design

Study or Subgroup	Triptan Events	Triptan Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
6.1.1 Cross-over						
Ahonen 2004	26	83	17	83	3.6%	1.53 [0.90 , 2.60]
Ahonen 2006	34	96	17	96	3.8%	2.00 [1.20 , 3.33]
Callenbach 2007	12	46	9	46	2.0%	1.33 [0.62 , 2.86]
Evers 2006	13	29	2	29	0.6%	6.50 [1.61 , 26.28]
Hämäläinen 1997b	5	23	2	23	0.5%	2.50 [0.54 , 11.60]
Lewis 2007	58	148	24	127	5.2%	2.07 [1.37 , 3.13]
Winner 1997	58	222	14	76	3.7%	1.42 [0.84 , 2.39]
Subtotal (95% CI)		**647**		**480**	**19.5%**	**1.81 [1.44 , 2.26]**
Total events:	206		85			
Heterogeneity: Tau² = 0.00; Chi² = 5.84, df = 6 (P = 0.44); I² = 0%						
Test for overall effect: Z = 5.13 (P < 0.00001)						
6.1.2 Parallel						
Fujita 2014	16	74	20	70	3.2%	0.76 [0.43 , 1.34]
Ho 2012	87	284	62	286	8.2%	1.41 [1.07 , 1.87]
Linder 2008	212	544	60	170	9.9%	1.10 [0.88 , 1.39]
NCT01211145	86	288	50	296	7.5%	1.77 [1.30 , 2.41]
Rothner 1997	52	226	16	74	4.0%	1.06 [0.65 , 1.75]
Rothner 1999a	43	208	10	35	3.1%	0.72 [0.40 , 1.30]
Rothner 1999b	9	62	3	30	0.8%	1.45 [0.42 , 4.98]
Rothner 1999c	11	66	5	36	1.3%	1.20 [0.45 , 3.18]
Rothner 2006	108	483	32	162	6.4%	1.13 [0.80 , 1.61]
Visser 2004a	91	233	75	240	9.3%	1.25 [0.98 , 1.60]
Winner 2000	116	377	32	130	6.8%	1.25 [0.89 , 1.75]
Winner 2002	48	149	40	142	6.4%	1.14 [0.81 , 1.62]
Winner 2006	191	483	68	242	9.9%	1.41 [1.12 , 1.77]
Winner 2007	32	144	20	133	3.9%	1.48 [0.89 , 2.45]
Subtotal (95% CI)		**3621**		**2046**	**80.5%**	**1.25 [1.12 , 1.39]**
Total events:	1102		493			
Heterogeneity: Tau² = 0.01; Chi² = 15.48, df = 13 (P = 0.28); I² = 16%						
Test for overall effect: Z = 4.16 (P < 0.0001)						
Total (95% CI)		**4268**		**2526**	**100.0%**	**1.33 [1.19 , 1.49]**
Total events:	1308		578			
Heterogeneity: Tau² = 0.02; Chi² = 29.96, df = 20 (P = 0.07); I² = 33%						
Test for overall effect: Z = 4.92 (P < 0.00001)						
Test for subgroup differences: Chi² = 8.47, df = 1 (P = 0.004), I² = 88.2%						



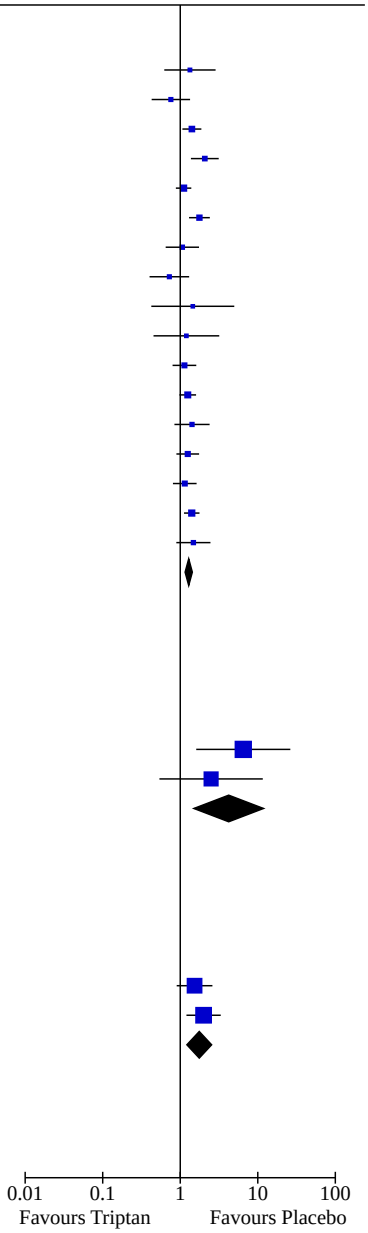
Analysis 6.2. Comparison 6: Triptans vs placebo in adolescents, sensitivity analysis, Outcome 2: Allocation concealment

Study or Subgroup	Triptan Events	Triptan Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
6.2.1 Low						
Ahonen 2004	26	83	17	83	11.2%	1.53 [0.90 , 2.60]
Ahonen 2006	34	96	17	96	11.8%	2.00 [1.20 , 3.33]
Evers 2006	13	29	2	29	2.5%	6.50 [1.61 , 26.28]
Fujita 2014	16	74	20	70	10.3%	0.76 [0.43 , 1.34]
Lewis 2007	58	148	24	127	14.5%	2.07 [1.37 , 3.13]
Winner 1997	58	222	14	76	11.4%	1.42 [0.84 , 2.39]
Winner 2000	116	377	32	130	17.1%	1.25 [0.89 , 1.75]
Winner 2006	191	483	68	242	21.1%	1.41 [1.12 , 1.77]
Subtotal (95% CI)		**1512**		**853**	**100.0%**	**1.50 [1.19 , 1.89]**
Total events:	512		194			
Heterogeneity: Tau² = 0.05; Chi² = 14.75, df = 7 (P = 0.04); I² = 53%						
Test for overall effect: Z = 3.39 (P = 0.0007)						
6.2.2 Unclear						
Callenbach 2007	12	46	9	46	2.0%	1.33 [0.62 , 2.86]
Ho 2012	87	284	62	286	14.1%	1.41 [1.07 , 1.87]
Hämäläinen 1997b	5	23	2	23	0.5%	2.50 [0.54 , 11.60]
Linder 2008	212	544	60	170	20.7%	1.10 [0.88 , 1.39]
NCT01211145	86	288	50	296	11.8%	1.77 [1.30 , 2.41]
Rothner 1997	52	226	16	74	4.7%	1.06 [0.65 , 1.75]
Rothner 1999a	43	208	10	35	3.4%	0.72 [0.40 , 1.30]
Rothner 1999b	9	62	3	30	0.8%	1.45 [0.42 , 4.98]
Rothner 1999c	11	66	5	36	1.2%	1.20 [0.45 , 3.18]
Rothner 2006	108	483	32	162	9.2%	1.13 [0.80 , 1.61]
Visser 2004a	91	233	75	240	18.0%	1.25 [0.98 , 1.60]
Winner 2002	48	149	40	142	9.2%	1.14 [0.81 , 1.62]
Winner 2007	32	144	20	133	4.5%	1.48 [0.89 , 2.45]
Subtotal (95% CI)		**2756**		**1673**	**100.0%**	**1.25 [1.12 , 1.40]**
Total events:	796		384			
Heterogeneity: Tau² = 0.00; Chi² = 12.32, df = 12 (P = 0.42); I² = 3%						
Test for overall effect: Z = 4.08 (P < 0.0001)						
Test for subgroup differences: Chi² = 1.85, df = 1 (P = 0.17), I² = 46.0%						



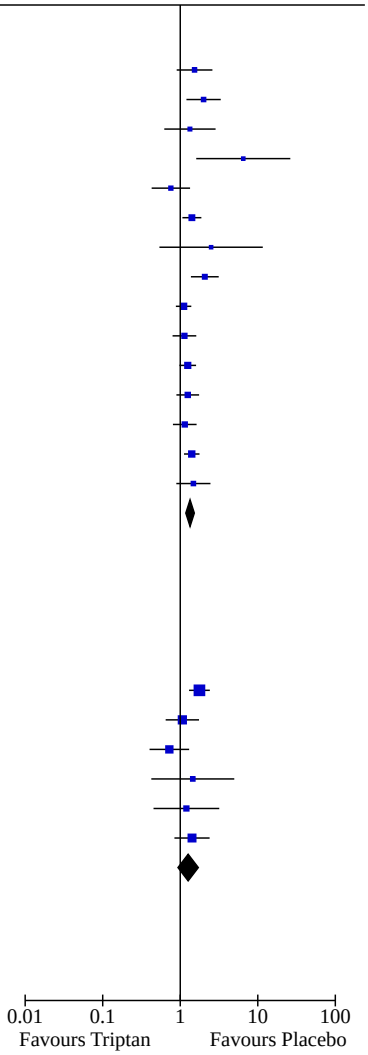
Analysis 6.3. Comparison 6: Triptans vs placebo in adolescents, sensitivity analysis, Outcome 3: Source of funding

Study or Subgroup	Triptan Events	Triptan Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
6.3.1 Pharmaceutical						
Callenbach 2007	12	46	9	46	1.8%	1.33 [0.62 , 2.86]
Fujita 2014	16	74	20	70	3.1%	0.76 [0.43 , 1.34]
Ho 2012	87	284	62	286	9.3%	1.41 [1.07 , 1.87]
Lewis 2007	58	148	24	127	5.4%	2.07 [1.37 , 3.13]
Linder 2008	212	544	60	170	12.0%	1.10 [0.88 , 1.39]
NCT01211145	86	288	50	296	8.3%	1.77 [1.30 , 2.41]
Rothner 1997	52	226	16	74	4.0%	1.06 [0.65 , 1.75]
Rothner 1999a	43	208	10	35	2.9%	0.72 [0.40 , 1.30]
Rothner 1999b	9	62	3	30	0.7%	1.45 [0.42 , 4.98]
Rothner 1999c	11	66	5	36	1.1%	1.20 [0.45 , 3.18]
Rothner 2006	108	483	32	162	6.8%	1.13 [0.80 , 1.61]
Visser 2004a	91	233	75	240	11.0%	1.25 [0.98 , 1.60]
Winner 1997	58	222	14	76	3.6%	1.42 [0.84 , 2.39]
Winner 2000	116	377	32	130	7.3%	1.25 [0.89 , 1.75]
Winner 2002	48	149	40	142	6.9%	1.14 [0.81 , 1.62]
Winner 2006	191	483	68	242	11.9%	1.41 [1.12 , 1.77]
Winner 2007	32	144	20	133	3.8%	1.48 [0.89 , 2.45]
Subtotal (95% CI)		**4037**		**2295**	**100.0%**	**1.29 [1.16 , 1.43]**
Total events:	1230		540			
Heterogeneity: Tau² = 0.01; Chi² = 21.07, df = 16 (P = 0.18); I² = 24%						
Test for overall effect: Z = 4.61 (P < 0.00001)						
6.3.2 Non-pharmaceutical						
Evers 2006	13	29	2	29	54.7%	6.50 [1.61 , 26.28]
Hämäläinen 1997b	5	23	2	23	45.3%	2.50 [0.54 , 11.60]
Subtotal (95% CI)		**52**		**52**	**100.0%**	**4.22 [1.50 , 11.84]**
Total events:	18		4			
Heterogeneity: Tau² = 0.00; Chi² = 0.83, df = 1 (P = 0.36); I² = 0%						
Test for overall effect: Z = 2.73 (P = 0.006)						
6.3.3 Unclear						
Ahonen 2004	26	83	17	83	47.9%	1.53 [0.90 , 2.60]
Ahonen 2006	34	96	17	96	52.1%	2.00 [1.20 , 3.33]
Subtotal (95% CI)		**179**		**179**	**100.0%**	**1.76 [1.22 , 2.54]**
Total events:	60		34			
Heterogeneity: Tau² = 0.00; Chi² = 0.51, df = 1 (P = 0.47); I² = 0%						
Test for overall effect: Z = 3.01 (P = 0.003)						
Test for subgroup differences: Chi² = 7.39, df = 2 (P = 0.02), I² = 73.0%						



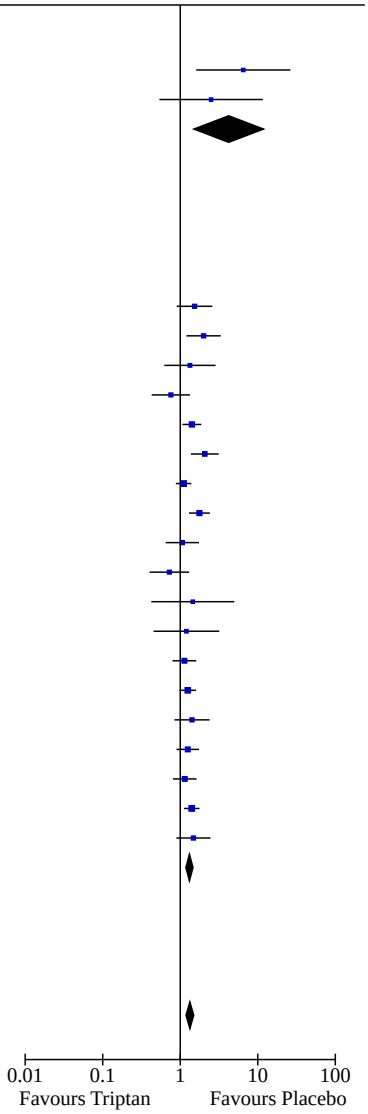
Analysis 6.4. Comparison 6: Triptans vs placebo in adolescents, sensitivity analysis, Outcome 4: Reported in a journal

Study or Subgroup	Triptan Events	Triptan Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
6.4.1 Journal report						
Ahonen 2004	26	83	17	83	4.5%	1.53 [0.90 , 2.60]
Ahonen 2006	34	96	17	96	4.8%	2.00 [1.20 , 3.33]
Callenbach 2007	12	46	9	46	2.4%	1.33 [0.62 , 2.86]
Evers 2006	13	29	2	29	0.8%	6.50 [1.61 , 26.28]
Fujita 2014	16	74	20	70	4.0%	0.76 [0.43 , 1.34]
Ho 2012	87	284	62	286	10.4%	1.41 [1.07 , 1.87]
Hämäläinen 1997b	5	23	2	23	0.7%	2.50 [0.54 , 11.60]
Lewis 2007	58	148	24	127	6.5%	2.07 [1.37 , 3.13]
Linder 2008	212	544	60	170	12.5%	1.10 [0.88 , 1.39]
Rothner 2006	108	483	32	162	8.0%	1.13 [0.80 , 1.61]
Visser 2004a	91	233	75	240	11.7%	1.25 [0.98 , 1.60]
Winner 2000	116	377	32	130	8.5%	1.25 [0.89 , 1.75]
Winner 2002	48	149	40	142	8.0%	1.14 [0.81 , 1.62]
Winner 2006	191	483	68	242	12.5%	1.41 [1.12 , 1.77]
Winner 2007	32	144	20	133	4.8%	1.48 [0.89 , 2.45]
Subtotal (95% CI)		**3196**		**1979**	**100.0%**	**1.34 [1.18 , 1.52]**
Total events:	1049		480			
Heterogeneity: Tau² = 0.02; Chi² = 21.59, df = 14 (P = 0.09); I² = 35%						
Test for overall effect: Z = 4.53 (P < 0.00001)						
6.4.2 Registry or abstract only						
NCT01211145	86	288	50	296	30.7%	1.77 [1.30 , 2.41]
Rothner 1997	52	226	16	74	20.4%	1.06 [0.65 , 1.75]
Rothner 1999a	43	208	10	35	16.6%	0.72 [0.40 , 1.30]
Rothner 1999b	9	62	3	30	5.3%	1.45 [0.42 , 4.98]
Rothner 1999c	11	66	5	36	7.9%	1.20 [0.45 , 3.18]
Winner 1997	58	222	14	76	19.2%	1.42 [0.84 , 2.39]
Subtotal (95% CI)		**1072**		**547**	**100.0%**	**1.26 [0.94 , 1.71]**
Total events:	259		98			
Heterogeneity: Tau² = 0.05; Chi² = 8.27, df = 5 (P = 0.14); I² = 40%						
Test for overall effect: Z = 1.53 (P = 0.13)						
Test for subgroup differences: Chi² = 0.12, df = 1 (P = 0.73), I² = 0%						



Analysis 6.5. Comparison 6: Triptans vs placebo in adolescents, sensitivity analysis, Outcome 5: Sample size

Study or Subgroup	Triptan Events	Triptan Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
6.5.1 Sample size ≤ 50						
Evers 2006	13	29	2	29	0.6%	6.50 [1.61 , 26.28]
Hämäläinen 1997b	5	23	2	23	0.5%	2.50 [0.54 , 11.60]
Subtotal (95% CI)		**52**		**52**	**1.2%**	**4.22 [1.50 , 11.84]**
Total events:	18		4			
Heterogeneity: Tau² = 0.00; Chi² = 0.83, df = 1 (P = 0.36); I² = 0%						
Test for overall effect: Z = 2.73 (P = 0.006)						
6.5.2 Sample size > 50						
Ahonen 2004	26	83	17	83	3.6%	1.53 [0.90 , 2.60]
Ahonen 2006	34	96	17	96	3.8%	2.00 [1.20 , 3.33]
Callenbach 2007	12	46	9	46	2.0%	1.33 [0.62 , 2.86]
Fujita 2014	16	74	20	70	3.2%	0.76 [0.43 , 1.34]
Ho 2012	87	284	62	286	8.2%	1.41 [1.07 , 1.87]
Lewis 2007	58	148	24	127	5.2%	2.07 [1.37 , 3.13]
Linder 2008	212	544	60	170	9.9%	1.10 [0.88 , 1.39]
NCT01211145	86	288	50	296	7.5%	1.77 [1.30 , 2.41]
Rothner 1997	52	226	16	74	4.0%	1.06 [0.65 , 1.75]
Rothner 1999a	43	208	10	35	3.1%	0.72 [0.40 , 1.30]
Rothner 1999b	9	62	3	30	0.8%	1.45 [0.42 , 4.98]
Rothner 1999c	11	66	5	36	1.3%	1.20 [0.45 , 3.18]
Rothner 2006	108	483	32	162	6.4%	1.13 [0.80 , 1.61]
Visser 2004a	91	233	75	240	9.3%	1.25 [0.98 , 1.60]
Winner 1997	58	222	14	76	3.7%	1.42 [0.84 , 2.39]
Winner 2000	116	377	32	130	6.8%	1.25 [0.89 , 1.75]
Winner 2002	48	149	40	142	6.4%	1.14 [0.81 , 1.62]
Winner 2006	191	483	68	242	9.9%	1.41 [1.12 , 1.77]
Winner 2007	32	144	20	133	3.9%	1.48 [0.89 , 2.45]
Subtotal (95% CI)		**4216**		**2474**	**98.8%**	**1.31 [1.18 , 1.46]**
Total events:	1290		574			
Heterogeneity: Tau² = 0.01; Chi² = 24.19, df = 18 (P = 0.15); I² = 26%						
Test for overall effect: Z = 5.07 (P < 0.00001)						
Total (95% CI)		**4268**		**2526**	**100.0%**	**1.33 [1.19 , 1.49]**
Total events:	1308		578			
Heterogeneity: Tau² = 0.02; Chi² = 29.96, df = 20 (P = 0.07); I² = 33%						
Test for overall effect: Z = 4.92 (P < 0.00001)						
Test for subgroup differences: Chi² = 4.84, df = 1 (P = 0.03), I² = 79.4%						



ADDITIONAL TABLES

Table 1. Summary of characteristics of included studies

Study characteristics	Criteria	N= 27[a]	%
Study design	Parallel	16	59%
	Cross-over	11	41%
Sponsorship	Pharmaceutical	19	70%
	Non-pharmaceutical	5	19%

Table 1. Summary of characteristics of included studies *(Continued)*

	Unclear	3	11%
Age inclusion criteria	Adolescents (12-17 years)	17	63%
	Children and adolescents	6	22%
	Children (< 12 years)	4	15%
Pain scale	4-point scale	21	78%
	5-faces scale	5	18%
	VAS	1	4%
Preventive medication permitted?	Yes	9	33%
	No	13	48%
	Unclear	5	19%
Route of delivery	Oral	19	70%
	Intranasal	8	30%
Medications	Paracetamol	1	4%
	Ibuprofen	3	7%
	Triptans	24	85%
	DHE	1	4%
Triptan medications	Almotriptan	1	4%
	Eletriptan	1	4%
	Naratriptan	1	4%
	Rizatriptan	4	17%
	Sumatriptan	12	50%
	Sumatriptan + naproxen sodium	1	4%
	Zolmitriptan	4	17%

DHE: dihydroergotamine; **VAS**: visual analogue scale.
[a]The total number of studies listed in Medications does not add up to 27 as two studies (Hämäläinen 1997a & Evers 2006) compared multiple medications.

Table 2. Summary table of included studies

Review Manager ID	Study design	Agent	Route	Child. (< 12 yrs)	Adolesc. (12-17 yrs)	Mean age	No	% Female
Paracetamol								
Hämäläinen 1997a	Cross-over	—	PO	Yes	Yes	10.7	80	50%
Ibuprofen								
Hämäläinen 1997a	Cross-over	—	PO	Yes	Yes	10.7	78	50%
Lewis 2002	Parallel	—	PO	Yes	No	9.0	84	ND
Evers 2006	Cross-over	—	PO	Yes	Yes	13.9	29	56%
Triptans (< 12 years)								
Ho 2012	Parallel	Rizatriptan	PO	Yes	NA	ND	200	44%
Ueberall 1999	Cross-over	Sumatriptan	IN	Yes	No	8.2	14	50%
Hämäläinen 2002	Cross-over	Sumatriptan	IN	Yes	No	9.7	59	54%
Triptans (12-17 years)								
Linder 2008	Parallel	Almotriptan	PO	No	Yes	14.4	714	60%
Winner 2007	Parallel	Eletriptan	PO	No	Yes	14.0	274	57%
Rothner 1997	Parallel	Naratriptan	PO	No	Yes	14.3	300	54%
Ho 2012	Parallel	Rizatriptan	PO	NA	Yes	ND	570	61%
Visser 2004a	Parallel	Rizatriptan	PO	No	Yes	14.2	476	55%
Winner 2002	Parallel	Rizatriptan	PO	No	Yes	14.0	296	54%
Ahonen 2006	Cross-over	Rizatriptan	PO	Yes	Yes	12.0	116	54%
Callenbach 2007	Cross-over	Sumatriptan	IN	No	Yes	13.6	46	78%

Table 2. Summary table of included studies *(Continued)*

Rothner 1999b	Parallel	Sumatriptan	PO	No	Yes	13.6	92	52%
Winner 2000	Parallel	Sumatriptan	IN	No	Yes	14.1	507	52%
Hämäläinen 1997b	Cross-over	Sumatriptan	PO	Yes	Yes	12.3	23	52%
Rothner 1999c	Parallel	Sumatriptan	PO	No	Yes	13.5	102	42%
Fujita 2014	Parallel	Sumatriptan	PO	Yes	Yes	14.1	144	58%
Winner 1997	Cross-over	Sumatriptan	PO	No	Yes	13.9	298	58%
Winner 2006	Parallel	Sumatriptan	IN	No	Yes	14.3	731	55%
Ahonen 2004	Cross-over	Sumatriptan	IN	Yes	Yes	12.4	94	46%
Rothner 1999a	Parallel	Sumatriptan	PO	No	Yes	14.1	273	57%
Derosier 2012	Parallel	Sumatriptan and Naproxen Sodium	PO	No	Yes	14.7	490	59%
Lewis 2007	Cross-over	Zolmitriptan	IN	No	Yes	14.2	171	57%
Evers 2006	Cross-over	Zolmitriptan	PO	Yes	Yes	13.9	29	56%
Rothner 2006	Parallel	Zolmitriptan	PO	No	Yes	14.2	696	59%
NCT01211145	Parallel	Zolmitriptan	IN	No	Yes	14	584	ND
Dihydroergotamine								
Hämäläinen 1997c	Cross-over	—	PO	Yes	Yes	10.3	13	38%

IN: intranasal; NA: not applicable; ND: no data available; No: total number in efficacy analysis (intention-to-treat when available); PO: per os (by mouth).

APPENDICES

Appendix 1. Complete Search Strategy

LITERATURE SEARCH—Drugs for the acute treatment of migraine in children and adolescents

Database	2008		2012		2013		2014		2016		Total	
	Number retrieved	After duplicates removed	Number retrieved	After duplicates removed	Number retrieved	After duplicates removed	Number retrieved	After duplicates removed	Number retrieved	After duplicates removed	Number retrieved	After duplicates removed
MEDLINE	2844	2742	639	616	90	75	—	—	326	231	3899	3664
MEDLINE In-Process	29	29	29	29	16	14	—	—	—	—	74	72
CCRT	153	126	153	126	10	2	—	—	—	—	316	254
CDSR DARE	664	650	664	650	324	169	—	—	—	—	1652	1469
IPA	109	27	40	10	7	4	—	—	—	—	156	41
PsycINFO	255	147	147	85	5	3	—	—	—	—	407	235
EMBASE	6357	5548	2884	2517	508	412	794	787	626	516	11,169	9780
CINAHL	712	190	263	70	31	21	—	—	—	—	1006	281
Total	**11,123**	**9459**	**4819**	**4103**	**991**	**700**	**794**	**787**	**952**	**747**	**18,679**	**15,796**

Searcher: Robin Featherstone

Requestor: Lawrence Richer

Date Submitted: 3 February 2016

Last update: 19 December 2014

Files submitted:

1. Richer-AcuteMigraine-Update_Feb2016.enlx

2. Richer-AcuteMigraine-Update_Feb2016.xlsx

Search Summary:

Database	Date Searched	Number Retrieved	After Duplicate Removal[a]
EMBASE	3 February 2016	626	516
MEDLINE	3 February 2016	326	231
Total		**952**	**747**

[a]Note: Removed any records retrieved by previous updates.

Database: EMBASE via Ovid 1996 to 2016 Week 05

Search Title: Richer_Acute_Migraine_2016Update

Strategy:

Migraine-related terms:

1. exp Headache Disorders/

2. vascular headache/

3. headache/

4. (migraine$ or headache$ or head-ache$ or cephalgia or cephalalgia).ti,ab.

5. or/1-4 (180,453)

Pharmaceutical related terms:

6. exp Drug Therapy/

7. (drug adj3 (therap$ or treatment?)).mp.

8. ((anti-migrain$ or antimigrain$) adj3 (therap$ or treatment?)).mp.

9. (ad or ae or dt or to).fs.

10. exp Treatment Outcome/

11. exp Analgesics/

12. "nonsteroidal anti-inflammatory agent?".mp.
13. "non-steroidal anti-inflammatory agent?".mp.
14. NSAID?.mp.
15. ibuprofen.mp.
16. fenoprofen.mp.
17. flurbiprofen.mp.
18. ketoprofen.mp.
19. ketorolac.mp.
20. diclofenac.mp.
21. etodolac.mp.
22. sulindac.mp.
23. diflunisal.mp.
24. naproxen.mp.
25. oxaprozin.mp.
26. tiaprofenic acid.mp.
27. mefenamic acid.mp.
28. indomethacin.mp.
29. tolmetin.mp.
30. celecoxib.mp.
31. meloxicam.mp.
32. piroxicam.mp.
33. tenoxicam.mp.
34. floctafenin$.mp.
35. nabumeton$.mp.
36. acetaminophen.mp.
37. paracetamol.mp.
38. ergot$ alkaloid?.mp.
39. ergotamin$.mp.
40. dihydroergotoxin$.mp.
41. dihydroergotamin$.mp.
42. DHE.mp.
43. ergoloid mesylates.mp.
44. methysergide.mp.
45. ziconotide.mp.

46. opioid$.mp.
47. opiate$.mp.
48. opium.mp.
49. meperidine.mp.
50. alfentan#l.mp.
51. fentan#l.mp.
52. rem#fentan#l.mp.
53. sufentan#l.mp.
54. levomethadyl.mp.
55. butorphanol.mp.
56. codein?.mp.
57. morphine.mp.
58. pentazocin$.mp.
59. (propoxyphen$ or dextro?propoxyphen$).mp.
60. nalbuphin$.mp.
61. hydromorphon$.mp.
62. oxycodon$.mp.
63. oxymorphon$.mp.
64. methadon$.mp.
65. butalbital.mp.
66. aspirin.mp.
67. acetylsalicylic acid.mp.
68. caffeine.mp.
69. "combination analgesic?".tw.
70. APAP.tw.
71. dichloralphenazone.mp.
72. isomethepten$.mp.
73. corticosteroid$.mp.
74. hydrocortisone.mp.
75. prednisolone.mp.
76. methylprednisolone.mp.
77. dexamethasone.mp.
78. tryptamin$.mp.
79. triptan?.mp.

80. sumatriptan.mp.

81. naratriptan.mp.

82. rizatriptan.mp.

83. zolmitriptan.mp.

84. almotriptan.mp.

85. eletriptan.mp.

86. frovatriptan.mp.

87. serotonin agonist?.mp.

88. ((5-hydroxytryptamine or 5-HT) adj2 agonist?).mp.

89. (antiemetic? or anti-emetic?).mp.

90. (antinauseant? or anti-nauseant?).mp.

91. chlorpromazine.mp.

92. prochlorperazine.mp.

93. perphenazine.mp.

94. trifluoperazine.mp.

95. (met#clopr#mide or metochlopramide).mp.

96. scopolamin$.mp.

97. dimenhydrinate.mp.

98. dronabinol.mp.

99. nabilon$.mp.

100. thiethylperazine.mp.

101. trimethobenzamide.mp.

102. ondansetron.mp.

103. granisetron.mp.

104. dolasetron.mp.

105. diphenhydramine.mp.

106. hydroxyzine.mp.

107. promethazine.mp.

108. Valproic Acid.mp.

109. valproate.mp.

110. divalproex sodium.mp.

111. Clonidine.mp.

112. fluid bolus.mp.

113. normal saline.mp.

114. magnesium.mp.

115. lidocaine.mp.

116. Botulinum Toxin Type A/

117. botulinium toxin.mp.

118. botox.mp.

119. oxygen.mp.

120. placebo$.mp.

121. or/6-120 [combination of all pharmaceutical treatments for migraine]

RCT filter:

122. random*.tw.

123. placebo*.mp.

124. double-blind*.tw.

125. or/122-124 [RCT filter from J Med Libr Assoc 2006]

Child related terms:

126. adolescent/

127. child/

128. newborn/

129. exp Pediatrics/

130. infant$.mp.

131. infancy.mp.

132. newborn$.mp.

133. baby.mp.

134. babies.mp.

135. neonat$.mp.

136. preterm$.mp.

137. prematur$.mp.

138. postmatur$.mp.

139. child$.mp.

140. kid.mp.

141. kids.mp.

142. toddler$.mp.

143. adolescen$.mp.

144. teen$.mp.

145. juvenile$.mp.

146. boy$.mp.

147. girl.mp.

148. girls.mp.

149. minor$.mp.

150. pubert$.mp.

151. pubescen$.mp.

152. pediatric$.mp.

153. paediatric$.mp.

154. peadiatric$.mp.

155. or/126-154 [child filter as per original search]

156. and/5,121,125,155 [combination of migraine + drugs + RCT + child]

157. limit 156 to em=201450-201605 (639)

158. remove duplicates from 157 (626)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present

Search Title: Richer_Acute_Migraine_2016Update_1

Strategy:

---

1. exp Headache Disorders/

2. vascular headaches/

3. headache/

4. (migraine$ or headache$ or head-ache$ or cephalgia or cephalalgia).ti,ab.

5. or/1-4

6. exp Drug Therapy/

7. (ad or ae or dt or to).fs.

8. exp Treatment Outcome/

9. exp Analgesics/

10. "nonsteroidal anti-inflammatory agent?".mp.

11. "non-steroidal anti-inflammatory agent?".mp.

12. NSAID?.mp.

13. ibuprofen.mp.

14. fenoprofen.mp.

15. flurbiprofen.mp.

16. ketoprofen.mp.

17. ketorolac.mp.
18. diclofenac.mp.
19. etodolac.mp.
20. sulindac.mp.
21. naproxen.mp.
22. tolmetin.mp.
23. oxaprozin.mp.
24. tenoxicam.mp.
25. tiaprofenic acid.mp.
26. mefenamic acid.mp.
27. ((acetylsalicylic adj1 acid) or aspirin).mp.
28. piroxicam.mp.
29. celecoxib.mp.
30. meloxicam.mp.
31. indomethacin.mp.
32. floctafenin$.mp.
33. nabumeton$.mp.
34. acetaminophen.mp.
35. paracetamol.mp.
36. ergotamin$.mp.
37. dihydroergotamin$.mp.
38. DHE.mp.
39. opioid$.mp.
40. opium.mp.
41. methadon$.mp.
42. meperidine.mp.
43. butorphanol.mp.
44. hydromorphon$.mp.
45. morphin$.mp.
46. codein?.mp.
47. butalbital.mp.
48. pentazocine.mp.
49. propoxyphene.mp.
50. nalbuphine.mp.

51. oxycodon$.mp.

52. ocymorphon$.mp.

53. alfentanil.mp.

54. fentanyl.mp.

55. sufentanil.mp.

56. caffeine.mp.

57. "combination analgesic?".tw.

58. tryptamines.mp.

59. triptan?.mp.

60. sumatriptan.mp.

61. naratriptan.mp.

62. rizatriptan.mp.

63. zolmitriptan.mp.

64. almotriptan.mp.

65. eletriptan.mp.

66. frovatriptan.mp.

67. serotonin agonist?.mp.

68. ((5-hydroxytriptamine or 5-HT) adj2 agonist?).mp.

69. (antiemetic? or anti-emetic?).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

70. (antinauseant? or anti-nauseant?).mp.

71. thiethylperazin$.mp.

72. trimethobenzamid$.mp.

73. scopolamin$.mp.

74. chlorpromazine.mp.

75. prochlorperazine.mp.

76. promethazin$.mp.

77. perphenazin$.mp.

78. trifluoperazin$.mp.

79. met#clopr#mide.mp.

80. ondansetron.mp.

81. granisetron.mp.

82. dolasetron.mp.

83. diphenhydramine.mp.

84. hydroxyzine.mp.

85. dimenhydrinate.mp.

86. dronabinol.mp.

87. nabilone.mp.

88. fluid bolus.mp.

89. normal saline.mp.

90. magnesium.mp.

91. lidocaine.mp.

92. corticosteroid$.mp.

93. prednisolone.mp.

94. solumedrol.mp.

95. dexamethason$.mp.

96. hydrocortisol.mp.

97. exp methylprednisolone/

98. Botulinum Toxin Type A/

99. botulinium toxin.mp.

100. botox.mp.

101. oxygen.mp.

102. clonidine.mp.

103. diflunisal.mp.

104. (levomethadyl or levo-methadyl).mp.

105. remifentanil.mp.

106. ziconotid$.mp.

107. placebo$.mp.

108. (antimigrain$ or anti-migrain$).mp.

109. divalproex.mp.

110. methysergid$.mp.

111. (ergoloid adj1 mesylate$).mp.

112. (abortive adj3 (therap$ or treatment$)).mp.

113. or/6-112

114. and/5,113

115. clinical trial.pt.

116. randomized controlled trial.pt.

117. randomi?ed.ti,ab.

118. placebo.ti,ab.

119. dt.fs.

120. randomly.ti,ab.

121. trial.ti,ab.

122. groups.ti,ab.

123. or/115-122

124. animals/

125. humans/

126. 124 not (124 and 125)

127. 123 not 126

128. exp Infant/

129. exp Child/

130. Adolescent/

131. Minors/

132. exp Puberty/

133. exp Pediatrics/

134. infant$.mp.

135. infancy.mp.

136. newborn$.mp.

137. baby.mp.

138. babies.mp.

139. neonat$.mp.

140. preterm$.mp.

141. prematur$.mp.

142. postmatur$.mp.

143. child$.mp.

144. kid.mp.

145. kids.mp.

146. toddler$.mp.

147. adolescen$.mp.

148. teen$.mp.

149. boy$.mp.

150. girl.mp.

151. minor$.mp.

152. pubert$.mp.

153. pubescen$.mp.

154. prepubescen$.mp.

155. pediatric$.mp.

156. paediatric$.mp.

157. peadiatric$.mp.

158. or/128-156

159. and/114,127,158

160. limit 159 to ed=20141219-20161231

161. remove duplicates from 160

-

Searcher: Robin Featherstone (original strategy Andrea Milne)

Requestor: Lawrence Richer

Date Requested: 3 December 2014

Date Submitted: 19 December 2014

NOTE: Last update: April 2013

Search Summary:

Database	Date Searched	Number Retrieved	After Duplicates Removed
EMBASE	19 December 2014	794	787

Database: EMBASE via Ovid 1996 to 2014 Week 50

Search Title: Migraine Acute – L Richer – Update 2.0 | EMBASE – 19 Dec 2014 – RF

Date Searched: 19 December 2014

Results:

Migraine related terms:

1. exp Headache Disorders/

2. vascular headache/

3. headache/

4. (migraine$ or headache$ or head-ache$ or cephalgia or cephalalgia).ti,ab.

5. or/1-4 (180,453)

Pharmaceutical related terms:

6. exp Drug Therapy/

7. (drug adj3 (therap$ or treatment?)).mp.

8. ((anti-migrain$ or antimigrain$) adj3 (therap$ or treatment?)).mp.

9. (ad or ae or dt or to).fs.

10. exp Treatment Outcome/

11. exp Analgesics/

12. "nonsteroidal anti-inflammatory agent?".mp.

13. "non-steroidal anti-inflammatory agent?".mp.

14. NSAID?.mp.

15. ibuprofen.mp.

16. fenoprofen.mp.

17. flurbiprofen.mp.

18. ketoprofen.mp.

19. ketorolac.mp.

20. diclofenac.mp.

21. etodolac.mp.

22. sulindac.mp.

23. diflunisal.mp.

24. naproxen.mp.

25. oxaprozin.mp.

26. tiaprofenic acid.mp.

27. mefenamic acid.mp.

28. indomethacin.mp.

29. tolmetin.mp.

30. celecoxib.mp.

31. meloxicam.mp.

32. piroxicam.mp.

33. tenoxicam.mp.

34. floctafenin$.mp.

35. nabumeton$.mp.

36. acetaminophen.mp.

37. paracetamol.mp.

38. ergot$ alkaloid?.mp.

39. ergotamin$.mp.

40. dihydroergotoxin$.mp.
41. dihydroergotamin$.mp.
42. DHE.mp.
43. ergoloid mesylates.mp.
44. methysergide.mp.
45. ziconotide.mp.
46. opioid$.mp.
47. opiate$.mp.
48. opium.mp.
49. meperidine.mp.
50. alfentan#l.mp.
51. fentan#l.mp.
52. rem#fentan#l.mp.
53. sufentan#l.mp.
54. levomethadyl.mp.
55. butorphanol.mp.
56. codein?.mp.
57. morphine.mp.
58. pentazocin$.mp.
59. (propoxyphen$ or dextro?propoxyphen$).mp.
60. nalbuphin$.mp.
61. hydromorphon$.mp.
62. oxycodon$.mp.
63. oxymorphon$.mp.
64. methadon$.mp.
65. butalbital.mp.
66. aspirin.mp.
67. acetylsalicylic acid.mp.
68. caffeine.mp.
69. "combination analgesic?".tw.
70. APAP.tw.
71. dichloralphenazone.mp.
72. isomethepten$.mp.
73. corticosteroid$.mp.

74. hydrocortisone.mp.

75. prednisolone.mp.

76. methylprednisolone.mp.

77. dexamethasone.mp.

78. tryptamin$.mp.

79. triptan?.mp.

80. sumatriptan.mp.

81. naratriptan.mp.

82. rizatriptan.mp.

83. zolmitriptan.mp.

84. almotriptan.mp.

85. eletriptan.mp.

86. frovatriptan.mp.

87. serotonin agonist?.mp.

88. ((5-hydroxytryptamine or 5-HT) adj2 agonist?).mp.

89. (antiemetic? or anti-emetic?).mp.

90. (antinauseant? or anti-nauseant?).mp.

91. chlorpromazine.mp.

92. prochlorperazine.mp.

93. perphenazine.mp.

94. trifluoperazine.mp.

95. (met#clopr#mide or metochlopramide).mp.

96. scopolamin$.mp.

97. dimenhydrinate.mp.

98. dronabinol.mp.

99. nabilon$.mp.

100. thiethylperazine.mp.

101. trimethobenzamide.mp.

102. ondansetron.mp.

103. granisetron.mp.

104. dolasetron.mp.

105. diphenhydramine.mp.

106. hydroxyzine.mp.

107. promethazine.mp.

108. Valproic Acid.mp.

109. valproate.mp.

110. divalproex sodium.mp.

111. Clonidine.mp.

112. fluid bolus.mp.

113. normal saline.mp.

114. magnesium.mp.

115. lidocaine.mp.

116. Botulinum Toxin Type A/

117. botulinium toxin.mp.

118. botox.mp.

119. oxygen.mp.

120. placebo$.mp.

121. or/6-120 [combination of all pharmaceutical treatments for migraine] (4,461,554)

RCT filter:

122. random*.tw.

123. placebo*.mp.

124. double-blind*.tw.

125. or/122-124 [RCT filter from J Med Libr Assoc 2006] (938,236)

Child related terms:

126. adolescent/

127. child/

128. newborn/

129. exp Pediatrics/

130. infant$.mp.

131. infancy.mp.

132. newborn$.mp.

133. baby.mp.

134. babies.mp.

135. neonat$.mp.

136. preterm$.mp.

137. prematur$.mp.

138. postmatur$.mp.

139. child$.mp.

140. kid.mp.

141. kids.mp.

142. toddler$.mp.

143. adolescen$.mp.

144. teen$.mp.

145. juvenile$.mp.

146. boy$.mp.

147. girl.mp.

148. girls.mp.

149. minor$.mp.

150. pubert$.mp.

151. pubescen$.mp.

152. pediatric$.mp.

153. paediatric$.mp.

154. peadiatric$.mp.

155. or/126-154 [child filter as per original search]

156. and/5,121,125,155 [combination of migrain + drugs + RCT + child] (6,679)

157. 2014*.dp,em,yr. [date of publication, entry date, year of publication limits] (1,525,211)

158. ("201318" or "201319" or 20132* or 20133* or 20134* or 20135*).em. [entry date limit] (1,086,901)

159. (or/157,158) and 156 [application of date limits] (931)

160. (1996* or 1997* or 1998* or 1999* or 2000* or 2001* or 2002* or 2003* or 2004* or 2005* or 2006* or 2007* or 2008* or 2009* or 2010* or 2011* or 2012* or 2013* or 2014*).dp,em,yr

161. 159 not 160 (794)

162. remove duplicates from 161 (787)

Search Summary (update after June 2008):

Review	Number Retrieved	After Duplicate Removal	Update Search Date	Number Retrieved	After Duplicate Removal
MEDLINE	639	616	29 April 2013	90	75
MEDLINE In-Process	29	29	29 April 2013	16	14
CCRT	153	127	29 April 2013	10	2
CDSR DARE	664	650	29 April 2013	324	169

(Continued)

IPA	40	10	29 April 2013	7	4
PsycINFO	147	85	29 April 2013	5	3
EMBASE	2,884	2,511	30 April 2013	508	411
CINAHL	213	70	30 April 2013	31	21
Total	**4769**	**4098**		**991**	**699**

Database: MEDLINE via Ovid <1946 to Present>

Search Title: Migraine Acute – L Richer – Update 1.0 | MEDLINE – 7 June 2012 – AM

Migraine related terms:

1. exp Headache Disorders/
2. vascular headaches/
3. headache/
4. (migraine$ or headache$ or head-ache$ or cephalgia or cephalalgia).ti,ab.
5. **or/1-4** (70,483)

Pharmaceutical related terms:

6. exp Drug Therapy/
7. (ad or ae or dt or to).fs.
8. exp Treatment Outcome/
9. exp Analgesics/
10. "nonsteroidal anti-inflammatory agent?".mp.
11. "non-steroidal anti-inflammatory agent?".mp.
12. NSAID?.mp.
13. ibuprofen.mp.
14. fenoprofen.mp.
15. flurbiprofen.mp.
16. ketoprofen.mp.
17. ketorolac.mp.
18. diclofenac.mp.
19. etodolac.mp.
20. sulindac.mp.
21. naproxen.mp.

(Continued)

22. tolmetin.mp.
23. oxaprozin.mp.
24. tenoxicam.mp.
25. tiaprofenic acid.mp.
26. mefenamic acid.mp.
27. ((acetylsalicylic adj1.acid) or aspirin).mp.
28. piroxicam.mp.
29. celecoxib.mp.
30. meloxicam.mp.
31. indomethacin.mp.
32. floctafenin$.mp.
33. nabumeton$.mp.
34. acetaminophen.mp.
35. paracetamol.mp.
36. ergotamin$.mp.
37. dihydroergotamin$.mp.
38. DHE.mp.
39. opioid$.mp.
40. opium.mp.
41. methadon$.mp.
42. meperidine.mp.
43. butorphanol.mp.
44. hydromorphon$.mp.
45. morphin$.mp.
46. codein?.mp.
47. butalbital.mp.
48. pentazocine.mp.
49. propoxyphene.mp.
50. nalbuphine.mp.
51. oxycodon$.mp.
52. ocymorphon$.mp.
53. alfentanil.mp.
54. fentanyl.mp.
55. sufentanil.mp.

(Continued)

56. caffeine.mp.
57. "combination analgesic?".tw.
58. tryptamines.mp.
59. triptan?.mp.
60. sumatriptan.mp.
61. naratriptan.mp.
62. rizatriptan.mp.
63. zolmitriptan.mp.
64. almotriptan.mp.
65. eletriptan.mp.
66. frovatriptan.mp.
67. serotonin agonist?.mp.
68. ((5-hydroxytriptamine or 5-HT) adj2 agonist?).mp.
69. (antiemetic? or anti-emetic?).mp.
70. (antinauseant? or anti-nauseant?).mp.
71. thiethylperazin$.mp.
72. trimethobenzamid$.mp.
73. scopolamin$.mp.
74. chlorpromazine.mp.
75. prochlorperazine.mp.
76. promethazin$.mp.
77. perphenazin$.mp.
78. trifluoperazin$.mp.
79. met#clopr#mide.mp.
80. ondansetron.mp.
81. granisetron.mp.
82. dolasetron.mp.
83. diphenhydramine.mp.
84. hydroxyzine.mp.
85. dimenhydrinate.mp.
86. dronabinol.mp.
87. nabilone.mp.
88. fluid bolus.mp.
89. normal saline.mp.

(Continued)

90. magnesium.mp.

91. lidocaine.mp.

92. corticosteroid$.mp.

93. prednisolone.mp.

94. solumedrol.mp.

95. dexamethason$.mp.

96. hydrocortisol.mp.

97. exp methylprednisolone/

98. Botulinum Toxin Type A/

99. botulinium toxin.mp.

100. botox.mp.

101. oxygen.mp.

102. clonidine.mp.

103. diflunisal.mp.

104. (levomethadyl or levo-methadyl).mp.

105. remifentanil.mp.

106. ziconotid$.mp.

107. placebo$.mp.

108. (antimigrain$ or anti-migrain$).mp.

109. divalproex.mp.

110. methysergid$.mp.

111. (ergoloid adj1 mesylate$).mp.

112. (abortive adj3 (therap$ or treatment$)).mp.

---

113. **or/6-112** (4,457,175)

RCT filter:

114. **and/5,113** (33,933)

115. randomized controlled trial.pt.

116. controlled clinical trial.pt.

117. randomized.ab.

118. placebo.ab.

119. clinical trials as topic.sh.

120. randomly.ab.

121. trial.ti.

122. **or/115-121** (762,426)

(Continued)

123. exp animals/ not humans.sh. (3,730,608)

124. **122 not 123** [Updated Cochrane RCT filter max specificity and precision] (702,878)

Child related terms:

125. exp Infant/

126. exp Child/

127. Adolescent/

128. Minors/

129. exp Puberty/

130. exp Pediatrics/

131. infant$.mp.

132. infancy.mp.

133. newborn$.mp.

134. baby.mp.

135. babies.mp.

136. neonat$.mp.

137. preterm$.mp.

138. prematur$.mp.

139. postmatur$.mp.

140. child$.mp.

141. kid.mp.

142. kids.mp.

143. toddler$.mp.

144. adolescen$.mp.

145. teen$.mp.

146. boy$.mp.

147. girl.mp.

148. minor$.mp.

149. pubert$.mp.

150. pubescen$.mp.

151. prepubescen$.mp.

152. pediatric$.mp.

153. paediatric$.mp.

154. peadiatric$.mp.

(Continued)

155. **or/125-154** (3,241,093)

156. **and/114,124,155** [combination of migraine + drug terms + RCT filter + child filter] (2,844)

Date limits for update:

157. limit 156 to ed="20080101-20120630" (639)

158. (2008* or 2009* or 201*).dp,ep,yr. [date of publication (.dp), electronic date of entry (.ep) and year (.yr) search fields for update] (3,078,760)

159. **and/156,158** [application of date restrictions to search results] (599)

160. **or/157,159** [combination of entry date and other date restrictions] (639)

Date limits for update 2013:

161. limit 156 to ed="20120630-20130430" (90)

162. (2012 jun* or 2013*).dp,ep. [date of publication (.dp), electronic date of entry (.ep)] (95,823)

163. and/156,162 [application of date restrictions to search results] (12)

164. or/161,163 [combination of date restrictions] (90)

Database: MEDLINE In-Process via Ovid <June 12, 2012>

Search Title: Migraine Acute – L Richer – Update 3.0 | Keyword Search – 8 June 2012 – AM

Migraine related terms:

1. (migraine$ or headache$ or head-ache$ or cephalgia or cephalalgia).mp. (3,432)

Pharmaceutical related terms:

2. (drug adj3 (therap$ or treatment?)).mp.

3. ((anti-migrain$ or antimigrain$) adj3 (therap$ or treatment?)).mp.

4. (treatment adj5.outcome).mp.

5. analgesi$.mp.

6. "nonsteroidal anti-inflammatory agent?".mp.

7. "non-steroidal anti-inflammatory agent?".mp.

8. NSAID?.mp.

9. ibuprofen.mp.

10. fenoprofen.mp.

11. flurbiprofen.mp.

12. ketoprofen.mp.

13. ketorolac.mp.

(Continued)

14. diclofenac.mp.
15. etodolac.mp.
16. sulindac.mp.
17. diflunisal.mp.
18. naproxen.mp.
19. oxaprozin.mp.
20. tiaprofenic acid.mp.
21. mefenamic acid.mp.
22. indomethacin.mp.
23. tolmetin.mp.
24. celecoxib.mp.
25. meloxicam.mp.
26. piroxicam.mp.
27. tenoxicam.mp.
28. floctafenin$.mp.
29. nabumeton$.mp.
30. acetaminophen.mp.
31. paracetamol.mp.
32. ergot$ alkaloid?.mp.
33. ergotamin$.mp.
34. dihydroergotoxin$.mp.
35. dihydroergotamin$.mp.
36. DHE.mp.
37. ergoloid mesylates.mp.
38. methysergide.mp.
39. ziconotide.mp.
40. opioid$.mp.
41. opiate$.mp.
42. opium.mp.
43. meperidine.mp.
44. alfentan#l.mp.
45. fentan#l.mp.
46. rem#fentan#l.mp.
47. sufentan#l.mp.

(Continued)

48. levomethadyl.mp.
49. butorphanol.mp.
50. codein?.mp.
51. morphine.mp.
52. pentazocin$.mp.
53. (propoxyphen$ or dextro?propoxyphen$).mp.
54. nalbuphin$.mp.
55. hydromorphon$.mp.
56. oxycodon$.mp.
57. oxymorphon$.mp.
58. methadon$.mp.
59. butalbital.mp.
60. aspirin.mp.
61. acetylsalicylic acid.mp.
62. caffeine.mp.
63. "combination analgesic?".tw.
64. APAP.tw.
65. dichloralphenazone.mp.
66. isomethepten$.mp.
67. corticosteroid$.mp.
68. hydrocortisone.mp.
69. prednisolone.mp.
70. methylprednisolone.mp.
71. dexamethasone.mp.
72. tryptamin$.mp.
73. triptan?.mp.
74. sumatriptan.mp.
75. naratriptan.mp.
76. rizatriptan.mp.
77. zolmitriptan.mp.
78. almotriptan.mp.
79. eletriptan.mp.
80. frovatriptan.mp.
81. serotonin agonist?.mp.

(Continued)

82. ((5-hydroxytryptamine or 5-HT) adj2 agonist?).mp.
83. (antiemetic? or anti-emetic?).mp.
84. (antinauseant? or anti-nauseant?).mp.
85. chlorpromazine.mp.
86. prochlorperazine.mp.
87. perphenazine.mp.
88. trifluoperazine.mp.
89. (met#clopr#mide or metochlopramide).mp.
90. scopolamin$.mp.
91. dimenhydrinate.mp.
92. dronabinol.mp.
93. nabilon$.mp.
94. thiethylperazine.mp.
95. trimethobenzamide.mp.
96. ondansetron.mp.
97. granisetron.mp.
98. dolasetron.mp.
99. diphenhydramine.mp.
100. hydroxyzine.mp.
101. promethazine.mp.
102. Valproic Acid.mp.
103. valproate.mp.
104. divalproex sodium.mp.
105. Clonidine.mp.
106. fluid bolus.mp.
107. normal saline.mp.
108. magnesium.mp.
109. lidocaine.mp.
110. botulinium toxin.mp.
111. botox.mp.
112. oxygen.mp.
113. placebo$.mp.

114. **or/2-113** [migraine drugs] (50,953)

RCT filter:

(Continued)

115. randomized controlled trial.pt.

116. controlled clinical trial.pt.

117. randomized.ab.

118. placebo.ab.

119. randomly.ab.

120. trial.ti.

121. **or/115-120** (27,679)

122. exp animals/ not humans.sh. (1)

123. **121.not 122** [Cochrane RCT filter, slightly modified for database] (27,679)

124. **and/1,114,123** [combination of migraine + drugs + RCT terms] (233)

Child related terms:

125. infant$.mp.

126. infancy.mp.

127. newborn$.mp.

128. baby.mp.

129. babies.mp.

130. neonat$.mp.

131. preterm$.mp.

132. prematur$.mp.

133. postmatur$.mp.

134. child$.mp.

135. kid.mp.

136. kids.mp.

137. toddler$.mp.

138. adolescen$.mp.

139. teen$.mp.

140. boy$.mp.

141. girl.mp.

142. girls.mp.

143. minor$.mp.

144. pubert$.mp.

145. pubescen$.mp.

146. pediatric$.mp.

147. paediatric$.mp.

(Continued)

148. peadiatric$.mp.

149. **or/125-148** [child filter] (66,612)

150. **and/124,149** [migraine + drug + RCT + child] (29)

Date limits for update:

151. (2008* or 2009* or 201*).ed,ep,up,yr. [entry date, e-pub date, update code, year of pub] (1,343,461)

152. **150 and 151** (29)

Date limits for update 2013:

153. ("2012" or "2013").ed,ep,up,yr. [entry date, e-pub date, update code, year of pub] (471,980)

154. and/150,153 (16)

Database Searched: Evidence Based Medicine Reviews via Ovid: **Cochrane Central Register of Controlled Trials** < May 2012 >

Search Title: Migraine Acute – L Richer – Update 1.1 | Cochrane – no SD filters – 11 June 2012 – AM

Migraine related terms:

1. exp Headache Disorders/

2. vascular headaches/

3. headache/

4. (migraine$ or headache$ or head-ache$ or cephalgia or cephalalgia).ti,ab.

5. **or/1-4** (8,180)

Pharmaceutical related terms:

6. exp Drug Therapy/

7. (ad or ae or dt or to).fs.

8. exp Treatment Outcome/

9. exp Analgesics/

10. "nonsteroidal anti-inflammatory agent?".mp.

11. "non-steroidal anti-inflammatory agent?".mp.

12. NSAID?.mp.

13. ibuprofen.mp.

14. fenoprofen.mp.

15. flurbiprofen.mp.

16. ketoprofen.mp.

(Continued)

17. ketorolac.mp.
18. diclofenac.mp.
19. etodolac.mp.
20. sulindac.mp.
21. naproxen.mp.
22. tolmetin.mp.
23. oxaprozin.mp.
24. tenoxicam.mp.
25. tiaprofenic acid.mp.
26. mefenamic acid.mp.
27. ((acetylsalicylic adj1 acid) or aspirin).mp.
28. piroxicam.mp.
29. celecoxib.mp.
30. meloxicam.mp.
31. indomethacin.mp.
32. floctafenin$.mp.
33. nabumeton$.mp.
34. acetaminophen.mp.
35. paracetamol.mp.
36. ergotamin$.mp.
37. dihydroergotamin$.mp.
38. DHE.mp.
39. opioid$.mp.
40. opium.mp.
41. methadon$.mp.
42. meperidine.mp.
43. butorphanol.mp.
44. hydromorphon$.mp.
45. morphin$.mp.
46. codein?.mp.
47. butalbital.mp.
48. pentazocine.mp.
49. propoxyphene.mp.
50. nalbuphine.mp.

(Continued)

51. oxycodon$.mp.
52. ocymorphon$.mp.
53. alfentanil.mp.
54. fentanyl.mp.
55. sufentanil.mp.
56. caffeine.mp.
57. "combination analgesic?".tw.
58. tryptamines.mp.
59. triptan?.mp.
60. sumatriptan.mp.
61. naratriptan.mp.
62. rizatriptan.mp.
63. zolmitriptan.mp.
64. almotriptan.mp.
65. eletriptan.mp.
66. frovatriptan.mp.
67. serotonin agonist?.mp.
68. ((5-hydroxytriptamine or 5-HT) adj2 agonist?).mp.
69. (antiemetic? or anti-emetic?).mp.
70. (antinauseant? or anti-nauseant?).mp.
71. thiethylperazin$.mp.
72. trimethobenzamid$.mp.
73. scopolamin$.mp.
74. chlorpromazine.mp.
75. prochlorperazine.mp.
76. promethazin$.mp.
77. perphenazin$.mp.
78. trifluoperazin$.mp.
79. met#clopr#mide.mp.
80. ondansetron.mp.
81. granisetron.mp.
82. dolasetron.mp.
83. diphenhydramine.mp.
84. hydroxyzine.mp.

(Continued)

85. dimenhydrinate.mp.

86. dronabinol.mp.

87. nabilone.mp.

88. fluid bolus.mp.

89. normal saline.mp.

90. magnesium.mp.

91. lidocaine.mp.

92. corticosteroid$.mp.

93. prednisolone.mp.

94. solumedrol.mp.

95. dexamethason$.mp.

96. hydrocortisol.mp.

97. exp methylprednisolone/

98. Botulinum Toxin Type A/

99. botulinium toxin.mp.

100. botox.mp.

101. oxygen.mp.

102. clonidine.mp.

103. diflunisal.mp.

104. (levomethadyl or levo-methadyl).mp.

105. remifentanil.mp.

106. ziconotid$.mp.

107. placebo$.mp.

108. (antimigrain$ or anti-migrain$).mp.

109. divalproex.mp.

110. methysergid$.mp.

111. (ergoloid adj1 mesylate$).mp.

112. (abortive adj3 (therap$ or treatment$)).mp.

---

113. **or/6-112** (335,914)

---

114. **and/5,113** (6,616)

Child related terms:

115. exp Infant/

116. exp Child/

117. Adolescent/

(Continued)

118. Minors/

119. exp Puberty/

120. exp Pediatrics/

121. infant$.mp.

122. infancy.mp.

123. newborn$.mp.

124. baby.mp.

125. babies.mp.

126. neonat$.mp.

127. preterm$.mp.

128. prematur$.mp.

129. postmatur$.mp.

130. child$.mp.

131. kid.mp.

132. kids.mp.

133. toddler$.mp.

134. adolescen$.mp.

135. teen$.mp.

136. boy$.mp.

137. girl.mp.

138. minor$.mp.

139. pubert$.mp.

140. pubescen$.mp.

141. prepubescen$.mp.

142. pediatric$.mp.

143. paediatric$.mp.

144. peadiatric$.mp.

---

145. **or/115-144** (136,786)

---

146. **and/114,145** [migraine + drugs + child] (2,107)

Removal of MEDLINE *records:*

147. limit 146 to medline records (1,954)

148. **146 not 147** (153)

Date limits for update:

(Continued)

149. (2008* or 2009* or 201*).up. (671,470)

150. **and/148-149** [application of update code limit] (153)

---

151. limit 148 to latest update (2)

152. (2012 jun* or 2013*).up. [update code limit] (27,314)

153. new.uf. [update flag for new articles] (30,970)

154. (152 or 153) and 148 [application of update code and update flag to results] (10)

155. or/151,154 [combination of update results] (10)

Database Searched: Evidence Based Medicine Reviews via Ovid

Cochrane Database of Systematic Reviews <20(2005 to May 2012>, **Database of Abstracts of Reviews of Effects** <2nd Quarter 2012>

Search Title: *Migraine Acute – L Richer – Update 3.2* | CCRT – 11 June 2012 – AM

Migraine related terms:

1. (migraine$ or headache$ or head-ache$ or cephalgia or cephalalgia).mp. (1,490)

Pharmaceutical related terms:

2. (drug adj3 (therap$ or treatment?)).mp.

3. ((anti-migrain$ or antimigrain$) adj3 (therap$ or treatment?)).mp.

4. (treatment adj5 outcome).mp.

5. analgesi$.mp.

6. "nonsteroidal anti-inflammatory agent?".mp.

7. "non-steroidal anti-inflammatory agent?".mp.

8. NSAID?.mp.

9. ibuprofen.mp.

10. fenoprofen.mp.

11. flurbiprofen.mp.

12. ketoprofen.mp.

13. ketorolac.mp.

14. diclofenac.mp.

15. etodolac.mp.

16. sulindac.mp.

17. diflunisal.mp.

18. naproxen.mp.

19. oxaprozin.mp.

(Continued)

20. tiaprofenic acid.mp.
21. mefenamic acid.mp.
22. indomethacin.mp.
23. tolmetin.mp.
24. celecoxib.mp.
25. meloxicam.mp.
26. piroxicam.mp.
27. tenoxicam.mp.
28. floctafenin$.mp.
29. nabumeton$.mp.
30. acetaminophen.mp.
31. paracetamol.mp.
32. ergot$ alkaloid?.mp.
33. ergotamin$.mp.
34. dihydroergotoxin$.mp.
35. dihydroergotamin$.mp.
36. DHE.mp.
37. ergoloid mesylates.mp.
38. methysergide.mp.
39. ziconotide.mp.
40. opioid$.mp.
41. opiate$.mp.
42. opium.mp.
43. meperidine.mp.
44. alfentan#l.mp.
45. fentan#l.mp.
46. rem#fentan#l.mp.
47. sufentan#l.mp.
48. levomethadyl.mp.
49. butorphanol.mp.
50. codein?.mp.
51. morphine.mp.
52. pentazocin$.mp.
53. (propoxyphen$ or dextro?propoxyphen$).mp.

(Continued)

54. nalbuphin$.mp.
55. hydromorphon$.mp.
56. oxycodon$.mp.
57. oxymorphon$.mp.
58. methadon$.mp.
59. butalbital.mp.
60. aspirin.mp.
61. acetylsalicylic acid.mp.
62. caffeine.mp.
63. "combination analgesic?".tw.
64. APAP.tw.
65. dichloralphenazone.mp.
66. isomethepten$.mp.
67. corticosteroid$.mp.
68. hydrocortisone.mp.
69. prednisolone.mp.
70. methylprednisolone.mp.
71. dexamethasone.mp.
72. tryptamin$.mp.
73. triptan?.mp.
74. sumatriptan.mp.
75. naratriptan.mp.
76. rizatriptan.mp.
77. zolmitriptan.mp.
78. almotriptan.mp.
79. eletriptan.mp.
80. frovatriptan.mp.
81. serotonin agonist?.mp.
82. ((5-hydroxytryptamine or 5-HT) adj2 agonist?).mp.
83. (antiemetic? or anti-emetic?).mp.
84. (antinauseant? or anti-nauseant?).mp.
85. chlorpromazine.mp.
86. prochlorperazine.mp.
87. perphenazine.mp.

(Continued)

88. trifluoperazine.mp.

89. (met#clopr#mide or metochlopramide).mp.

90. scopolamin$.mp.

91. dimenhydrinate.mp.

92. dronabinol.mp.

93. nabilon$.mp.

94. thiethylperazine.mp.

95. trimethobenzamide.mp.

96. ondansetron.mp.

97. granisetron.mp.

98. dolasetron.mp.

99. diphenhydramine.mp.

100. hydroxyzine.mp.

101. promethazine.mp.

102. Valproic Acid.mp.

103. valproate.mp.

104. divalproex sodium.mp.

105. Clonidine.mp.

106. fluid bolus.mp.

107. normal saline.mp.

108. magnesium.mp.

109. lidocaine.mp.

110. botulinium toxin.mp.

111. botox.mp.

112. oxygen.mp.

113. placebo$.mp.

---

114. **or/2-113** [migraine drugs] (16,264)

---

115. **and/1,114** [combination of migraine + drugs] (1,414)

Child related terms:

116. infant$.mp.

117. infancy.mp.

118. newborn$.mp.

119. baby.mp.

120. babies.mp.

(Continued)

121. neonat$.mp.

122. preterm$.mp.

123. prematur$.mp.

124. postmatur$.mp.

125. child$.mp.

126. kid.mp.

127. kids.mp.

128. toddler$.mp.

129. adolescen$.mp.

130. teen$.mp.

131. boy$.mp.

132. girl.mp.

133. girls.mp.

134. minor$.mp.

135. pubert$.mp.

136. pubescen$.mp.

137. pediatric$.mp.

138. paediatric$.mp.

139. peadiatric$.mp.

---

140. **or/116-139** [child filter] (9,102)

---

141. **and/115,140** [migraine + drug + RCT + child] (898)

---

142. remove duplicates from 141 (898)

Removal of articles which are protocols only:

143. limit 142 to protocols [Limit not valid in DARE; records were retained] (234)

144. **142 not 143** (664)

Date limits for update:

145. limit 144to last 5years (493)

146. (2008* or 2009* or 201*).up. (7,498)

147. **and/144,146** (664)

148. **145 or 147** (664)

Date limits for update 2013:

149. (2012 jun* or 2013*).up. [update code limit] (859)

150. new.uf. [update flag for new articles] (4,557)

(Continued)

151. (149 or 150) and 144 [application of update codes to original results] (324)

Database: International Pharmaceutical Abstracts via Ovid < 1970 to May 2012 >

Search Title: Migraine Acute – L Richer – Update 3.1 | IPA – Keyword w/o pt terms – 11 June 2012 – AM

Migraine related terms:

1. (migraine$ or headache$ or head-ache$ or cephalgia or cephalalgia).mp. (3,917)

Pharmaceutical related terms:

2. (drug adj3 (therap$ or treatment?)).mp.
3. ((anti-migrain$ or antimigrain$) adj3 (therap$ or treatment?)).mp.
4. (treatment adj5 outcome).mp.
5. analgesi$.mp.
6. "nonsteroidal anti-inflammatory agent?".mp.
7. "non-steroidal anti-inflammatory agent?".mp.
8. NSAID?.mp.
9. ibuprofen.mp.
10. fenoprofen.mp.
11. flurbiprofen.mp.
12. ketoprofen.mp.
13. ketorolac.mp.
14. diclofenac.mp.
15. etodolac.mp.
16. sulindac.mp.
17. diflunisal.mp.
18. naproxen.mp.
19. oxaprozin.mp.
20. tiaprofenic acid.mp.
21. mefenamic acid.mp.
22. indomethacin.mp.
23. tolmetin.mp.
24. celecoxib.mp.
25. meloxicam.mp.

(Continued)

26. piroxicam.mp.
27. tenoxicam.mp.
28. floctafenin$.mp.
29. nabumeton$.mp.
30. acetaminophen.mp.
31. paracetamol.mp.
32. ergot$ alkaloid?.mp.
33. ergotamin$.mp.
34. dihydroergotoxin$.mp.
35. dihydroergotamin$.mp.
36. DHE.mp.
37. ergoloid mesylates.mp.
38. methysergide.mp.
39. ziconotide.mp.
40. opioid$.mp.
41. opiate$.mp.
42. opium.mp.
43. meperidine.mp.
44. alfentan#l.mp.
45. fentan#l.mp.
46. rem#fentan#l.mp.
47. sufentan#l.mp.
48. levomethadyl.mp.
49. butorphanol.mp.
50. codein?.mp.
51. morphine.mp.
52. pentazocin$.mp.
53. (propoxyphen$ or dextro?propoxyphen$).mp.
54. nalbuphin$.mp.
55. hydromorphon$.mp.
56. oxycodon$.mp.
57. oxymorphon$.mp.
58. methadon$.mp.
59. butalbital.mp.

(Continued)

60. aspirin.mp.
61. acetylsalicylic acid.mp.
62. caffeine.mp.
63."combination analgesic?".tw.
64. APAP.tw.
65. dichloralphenazone.mp.
66. isomethepten$.mp.
67. corticosteroid$.mp.
68. hydrocortisone.mp.
69. prednisolone.mp.
70. methylprednisolone.mp.
71. dexamethasone.mp.
72. tryptamin$.mp.
73. triptan?.mp.
74. sumatriptan.mp.
75. naratriptan.mp.
76. rizatriptan.mp.
77. zolmitriptan.mp.
78. almotriptan.mp.
79. eletriptan.mp.
80. frovatriptan.mp.
81. serotonin agonist?.mp.
82. ((5-hydroxytryptamine or 5-HT) adj2 agonist?).mp.
83. (antiemetic? or anti-emetic?).mp.
84. (antinauseant? or anti-nauseant?).mp.
85. chlorpromazine.mp.
86. prochlorperazine.mp.
87. perphenazine.mp.
88. trifluoperazine.mp.
89. (met#clopr#mide or metochlopramide).mp.
90. scopolamin$.mp.
91. dimenhydrinate.mp.
92. dronabinol.mp.
93. nabilon$.mp.

(Continued)

94. thiethylperazine.mp.

95. trimethobenzamide.mp.

96. ondansetron.mp.

97. granisetron.mp.

98. dolasetron.mp.

99. diphenhydramine.mp.

100. hydroxyzine.mp.

101. promethazine.mp.

102. Valproic Acid.mp.

103. valproate.mp.

104. divalproex sodium.mp.

105. Clonidine.mp.

106. fluid bolus.mp.

107. normal saline.mp.

108. magnesium.mp.

109. lidocaine.mp.

110. botulinium toxin.mp.

111. botox.mp.

112. oxygen.mp.

113. placebo$.mp.

---

114. **or/2-113** [migraine drugs] (97,647)

RCT filter:

115. randomized.ab.

116. placebo.ab.

117. randomly.ab.

118. trial*.tw.

---

119. **or/115-118** (59,621)

---

120. **and/1,114,119** [combination of migraine + drugs + RCT terms] (1,011)

Child related terms:

121. infant$.mp.

122. infancy.mp.

123. newborn$.mp.

124. baby.mp.

(Continued)

125. babies.mp.

126. neonat$.mp.

127. preterm$.mp.

128. prematur$.mp.

129. postmatur$.mp.

130. child$.mp.

131. kid.mp.

132. kids.mp.

133. toddler$.mp.

134. adolescen$.mp.

135. teen$.mp.

136. boy$.mp.

137. girl.mp.

138. girls.mp.

139. minor$.mp.

140. pubert$.mp.

141. pubescen$.mp.

142. pediatric$.mp.

143. paediatric$.mp.

144. peadiatric$.mp.

145. **or/121-144** [child filter] (36,856)

146. **and/120,145** [migraine + drug + RCT + child] (109)

Date limits for update:

147. (2008* or 2009* or 201*).ed,ep,up,yr. [entry date, e-pub date, update code, year of pub] (87,846)

148. **146 and 147** (40)

149. (2012* or 2013*).em. [entry month date limit] (27,810)

150. and/146,149 [application of entry month date limit] (7)

Database: PsycINFO via Ovid < 1806 to June Week 1 2012 >

Search Title: Migraine Acute – L Richer – Update 4.0 | PsycINFO – 12 June 2012 – AM

Migraine related terms:

(Continued)

1. headache/
2. migraine/
3. muscle contraction headache/
4. (migraine$ or headache$ or head-ache$ or cephalgia or cephalalgia).ti,ab.

5. **or/1-4** (15,618)

Pharmaceutical related terms:

6. Drug Therapy/
7. exp drugs/
8. exp "side effects (drug)"/
9. (drug adj3 (therap$ or treatment?)).mp.
10. ((anti-migrain$ or antimigrain$) adj3 (therap$ or treatment?)).mp.
11. treatment outcomes/
12. (treatment adj5 outcome).mp.
13. analgesi$.mp.
14. "nonsteroidal anti-inflammatory agent?".mp.
15. "non-steroidal anti-inflammatory agent?".mp.
16. NSAID?.mp.
17. ibuprofen.mp.
18. fenoprofen.mp.
19. flurbiprofen.mp.
20. ketoprofen.mp.
21. ketorolac.mp.
22. diclofenac.mp.
23. etodolac.mp.
24. sulindac.mp.
25. diflunisal.mp.
26. naproxen.mp.
27. oxaprozin.mp.
28. tiaprofenic acid.mp.
29. mefenamic acid.mp.
30. indomethacin.mp.
31. tolmetin.mp.
32. celecoxib.mp.
33. meloxicam.mp.

(Continued)

34. piroxicam.mp.
35. tenoxicam.mp.
36. floctafenin$.mp.
37. nabumeton$.mp.
38. acetaminophen.mp.
39. paracetamol.mp.
40. ergot$ alkaloid?.mp.
41. ergotamin$.mp.
42. dihydroergotoxin$.mp.
43. dihydroergotamin$.mp.
44. DHE.mp.
45. ergoloid mesylates.mp.
46. methysergide.mp.
47. ziconotide.mp.
48. opioid$.mp.
49. opiate$.mp.
50. opium.mp.
51. meperidine.mp.
52. alfentan#l.mp.
53. fentan#l.mp.
54. rem#fentan#l.mp.
55. sufentan#l.mp.
56. levomethadyl.mp.
57. butorphanol.mp.
58. codein?.mp.
59. morphine.mp.
60. pentazocin$.mp.
61. (propoxyphen$ or dextro?propoxyphen$).mp.
62. nalbuphin$.mp.
63. hydromorphon$.mp.
64. oxycodon$.mp.
65. oxymorphon$.mp.
66. methadon$.mp.
67. butalbital.mp.

(Continued)

68. aspirin.mp.
69. acetylsalicylic acid.mp.
70. caffeine.mp.
71. "combination analgesic?".tw.
72. APAP.tw.
73. dichloralphenazone.mp.
74. isomethepten$.mp.
75. corticosteroid$.mp.
76. hydrocortisone.mp.
77. prednisolone.mp.
78. methylprednisolone.mp.
79. dexamethasone.mp.
80. tryptamin$.mp.
81. triptan?.mp.
82. sumatriptan.mp.
83. naratriptan.mp.
84. rizatriptan.mp.
85. zolmitriptan.mp.
86. almotriptan.mp.
87. eletriptan.mp.
88. frovatriptan.mp.
89. serotonin agonist?.mp.
90. ((5-hydroxytryptamine or 5-HT) adj2 agonist?).mp.
91. (antiemetic? or anti-emetic?).mp.
92. (antinauseant? or anti-nauseant?).mp.
93. chlorpromazine.mp.
94. prochlorperazine.mp.
95. perphenazine.mp.
96. trifluoperazine.mp.
97. (met#clopr#mide or metochlopramide).mp.
98. scopolamin$.mp.
99. dimenhydrinate.mp.
100. dronabinol.mp.
101. nabilon$.mp.

(Continued)

102. thiethylperazine.mp.

103. trimethobenzamide.mp.

104. ondansetron.mp.

105. granisetron.mp.

106. dolasetron.mp.

107. diphenhydramine.mp.

108. hydroxyzine.mp.

109. promethazine.mp.

110. Valproic Acid.mp.

111. valproate.mp.

112. divalproex sodium.mp.

113. Clonidine.mp.

114. fluid bolus.mp.

115. normal saline.mp.

116. magnesium.mp.

117. lidocaine.mp.

118. botulinium toxin.mp.

119. botox.mp.

120. oxygen.mp.

121. placebo$.mp.

122. **or/6-121** [drug terms] (310,358)

RCT filter:

123. double-blind.tw.

124. random* assigned.tw.

125. control*.tw.

---

126. **or/123-125** [HIRU max sensivity/specificity for RCTs] (439,506)

---

127. **and/5,122,126** [sensivity/specificity filter] (1,981)

Child related terms:

128. infant$.mp.

129. infancy.mp.

130. newborn$.mp.

131. baby.mp.

132. babies.mp.

(Continued)

133. neonat$.mp.

134. preterm$.mp.

135. prematur$.mp.

136. postmatur$.mp.

137. child$.mp.

138. kid.mp.

139. kids.mp.

140. toddler$.mp.

141. adolescen$.mp.

142. teen$.mp.

143. boy$.mp.

144. girl.mp.

145. girls.mp.

146. minor$.mp.

147. pubert$.mp.

148. pubescen$.mp.

149. pediatric$.mp.

150. paediatric$.mp.

151. peadiatric$.mp.

---

152. **or/128-151** (717,968)

---

153. **and/127,152** [sensitivity/specificity filter] (255)

Date limits for update:

154. limit 153 to yr="2008-Current" (107)

155. (2008* or 2009* or 201*).yr,dp,up. [year of publication, date of publication, update code search] (803,770)

---

156. **and/153,155** [application of date limits] (147)

157. **or/154,156** [ORing both date limits] (147)

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158. (2012 jun* or 2013*).dp,up. [date of publication, update code search] (62,816)

159. and/153,158 [application of date limits] (5)

Database: EMBASE via Ovid <1980 to present>

Search Title: Migraine Acute – L Richer – Update 2.0 | EMBASE – 8 June 2012 – AM

Migraine related terms:

1. exp Headache Disorders/

2. vascular headache/

3. headache/

4. (migraine$ or headache$ or head-ache$ or cephalgia or cephalalgia).ti,ab.

5. **or/1-4** (188,282)

Pharmaceutical related terms:

6. exp Drug Therapy/

7. (drug adj3 (therap$ or treatment?)).mp.

8. ((anti-migrain$ or antimigrain$) adj3 (therap$ or treatment?)).mp.

9. (ad or ae or dt or to).fs.

10. exp Treatment Outcome/

11. exp Analgesics/

12. "nonsteroidal anti-inflammatory agent?".mp.

13. "non-steroidal anti-inflammatory agent?".mp.

14. NSAID?.mp.

15. ibuprofen.mp.

16. fenoprofen.mp.

17. flurbiprofen.mp.

18. ketoprofen.mp.

19. ketorolac.mp.

20. diclofenac.mp.

21. etodolac.mp.

22. sulindac.mp.

23. diflunisal.mp.

24. naproxen.mp.

25. oxaprozin.mp.

26. tiaprofenic acid.mp.

27. mefenamic acid.mp.

28. indomethacin.mp.

29. tolmetin.mp.

30. celecoxib.mp.

31. meloxicam.mp.

(Continued)

32. piroxicam.mp.
33. tenoxicam.mp.
34. floctafenin$.mp.
35. nabumeton$.mp.
36. acetaminophen.mp.
37. paracetamol.mp.
38. ergot$ alkaloid?.mp.
39. ergotamin$.mp.
40. dihydroergotoxin$.mp.
41. dihydroergotamin$.mp.
42. DHE.mp.
43. ergoloid mesylates.mp.
44. methysergide.mp.
45. ziconotide.mp.
46. opioid$.mp.
47. opiate$.mp.
48. opium.mp.
49. meperidine.mp.
50. alfentan#l.mp.
51. fentan#l.mp.
52. rem#fentan#l.mp.
53. sufentan#l.mp.
54. levomethadyl.mp.
55. butorphanol.mp.
56. codein?.mp.
57. morphine.mp.
58. pentazocin$.mp.
59. (propoxyphen$ or dextro?propoxyphen$).mp.
60. nalbuphin$.mp.
61. hydromorphon$.mp.
62. oxycodon$.mp.
63. oxymorphon$.mp.
64. methadon$.mp.
65. butalbital.mp.

(Continued)

66. aspirin.mp.
67. acetylsalicylic acid.mp.
68. caffeine.mp.
69. "combination analgesic?".tw.
70. APAP.tw.
71. dichloralphenazone.mp.
72. isomethepten$.mp.
73. corticosteroid$.mp.
74. hydrocortisone.mp.
75. prednisolone.mp.
76. methylprednisolone.mp.
77. dexamethasone.mp.
78. tryptamin$.mp.
79. triptan?.mp.
80. sumatriptan.mp.
81. naratriptan.mp.
82. rizatriptan.mp.
83. zolmitriptan.mp.
84. almotriptan.mp.
85. eletriptan.mp.
86. frovatriptan.mp.
87. serotonin agonist?.mp.
88. ((5-hydroxytryptamine or 5-HT) adj2 agonist?).mp.
89. (antiemetic? or anti-emetic?).mp.
90. (antinauseant? or anti-nauseant?).mp.
91. chlorpromazine.mp.
92. prochlorperazine.mp.
93. perphenazine.mp.
94. trifluoperazine.mp.
95. (met#clopr#mide or metochlopramide).mp.
96. scopolamin$.mp.
97. dimenhydrinate.mp.
98. dronabinol.mp.
99. nabilon$.mp.

(Continued)

100. thiethylperazine.mp.

101. trimethobenzamide.mp.

102. ondansetron.mp.

103. granisetron.mp.

104. dolasetron.mp.

105. diphenhydramine.mp.

106. hydroxyzine.mp.

107. promethazine.mp.

108. Valproic Acid.mp.

109. valproate.mp.

110. divalproex sodium.mp.

111. Clonidine.mp.

112. fluid bolus.mp.

113. normal saline.mp.

114. magnesium.mp.

115. lidocaine.mp.

116. Botulinum Toxin Type A/

117. botulinium toxin.mp.

118. botox.mp.

119. oxygen.mp.

120. placebo$.mp.

---

121. **or/6-120** [combination of all possible pharmaceutical treatments for migraine] (5,743,355)

RCT filter:

122. random*.tw.

123. placebo*.mp.

124. double-blind*.tw.

---

125. **or/122-124** [RCT filter from J Med Libr Assoc 2006] (907,731)

Child related terms:

126. adolescent/

127. child/

128. newborn/

129. exp Pediatrics/

130. infant$.mp.

(Continued)

131. infancy.mp.

132. newborn$.mp.

133. baby.mp.

134. babies.mp.

135. neonat$.mp.

136. preterm$.mp.

137. prematur$.mp.

138. postmatur$.mp.

139. child$.mp.

140. kid.mp.

141. kids.mp.

142. toddler$.mp.

143. adolescen$.mp.

144. teen$.mp.

145. juvenile$.mp.

146. boy$.mp.

147. girl.mp.

148. girls.mp.

149. minor$.mp.

150. pubert$.mp.

151. pubescen$.mp.

152. pediatric$.mp.

153. paediatric$.mp.

154. peadiatric$.mp.

155. **or/126-154** [child filter as per original search]

156. **and/5,121,125,155** [combination of migrain + drugs + RCT + child] (6,357)

157. (2008* or 2009* or 201*).dp,em,yr. [date of publication, entry date, year of publication limits] (4,936,810)

158. **and/156-157** [application of date limits] (2,884)

Update search limits for 2013:

159. (2012 jun* or 2013*).dp. [date of publication limit] (24,334)

160. (20122* or 20123* or 20124* or 20125* or 2013*).em. [entry date limit] (1,247,362)

161. (or/159-160) and 156 [application of date limits] (508)

Database: CINAHL Plus with Full Text via Ebsco <1937 to present>

Search Title: Pediatric Migraine – CINAHL – Update – 12 June 2012 – AM

Limiters - Published Date from: 20120601-20130531 (31)

S17=S16 Limiters - Published Date from: 20080101-20120631 (263)

S16=**S1 and S2 and S14 and S15** (712)

Child related terms:

S15=((MH "Infant+") or (MH "Child+") or (MH "Adolescence") or (MH "Puberty+") or (MH "Pediatrics+") or infant* or infanc* or newborn* or baby or neonat* or preterm* or prematur* or postmatur* or child* or kid or kids or toddler* or adolescen* or teen* or boy* or girl or girls* or minor* or pubert* or pubescen* or pediatric* or paediatric* or peadiatric*) (601,431)

S14=**S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13** (807,111)

RCT filter:

S13=TX allocat* random*

S12=MH "Quantitative Studies"

S11=(MH "Placebos")

S10=TX placebo*

S9=TX random* allocat*

S8=(MH "Random Assignment")

S7=TX randomi* control* trial*

S6=TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*))

S5=TX clinic* n1 trial*

S4=PT Clinical trial

S3=(MH "Clinical Trials+")

Pharmaceutical related terms:

S2=((MH "Drug Therapy+") or (MH "Drug Therapy, Combination+") or (MH "Drug Combinations+") or (MH "Drug Therapy+") or MH "Drug Therapy, Combination+" or MH "Drug Combinations+" or drug w3 therap* or drug w3 treatment* or anti-migrain* w3 therap* or antimigrain* w3 treatment* or (MH "Treatment Outcomes+") or (MH "Analgesics+") or "nonsteroidal anti-inflammatory agent?" or "non-steroidal anti-inflammatory agent?" or ibuprofen or fenoprofen or flurbiprofen or Ketorolac or Diclofenac or Etodolac or Sulindac or Diflunisal or Naproxen or Oxaprozin or "tiaprofenic acid" or "mefenamic acid" or Indomethacin or Tolmetin or Celecoxib) or (Meloxicam or Piroxicam or Tenoxicam or Floctafenin* or nabumeton* or acetaminophen or ergot* w1 alkaloid* or ergotamin* or dihydroergotoxin* or dihydroergotamin* or DHE or ergoloid w1 mesylates or methysergide or ziconotide or opioid* or opiate*) or (opium or alfentan?l or fentan?l or rem?fentan?l or sufentan?l or levomethadyl or butorphanol or codein* or morphine or pentazocin* or propoxyphen* or dextro-propoxyphen* or dextropropoxyphen* or nalbuphin* or hydromorphon* or oxycodon*) (425780)

Migraine related terms:

S1=(MH "Headache+" or MH "Vascular Headache+") or TI (migraine* or headache* or head-ache* or cephalgia or cephalalgia) or AB (migraine* or headache* or head-ache* or cephalgia or cephalalgia) (18,833)

WHAT'S NEW

Date	Event	Description
29 October 2020	Review declared as stable	See Published notes.

HISTORY

Protocol first published: Issue 2, 2005
Review first published: Issue 4, 2016

Date	Event	Description
17 October 2018	Review declared as stable	See Published notes.
1 September 2010	Feedback has been incorporated	Incorporated feedback from Editorial review and updated search.
15 May 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Lawrence Richer - protocol development, review of publications, data entry, analysis, report writing, presentation of findings, updates to report.

Meghan Linsdell - review of publications, data abstraction, data entry, review of report, updates to report.

Lori Billinghurst - protocol development, review and selection of publications, presentation of findings.

Kelly Russell - data abstraction, report writing, review of report.

Ben Vandermeer - data abstraction, statistical analysis, report writing.

Tamara Durec and Ellen Crumley - development of publication database search.

Lisa Hartling - protocol development, review of report.

Terry Klassen - protocol development, review of report.

DECLARATIONS OF INTEREST

Lawrence Richer: no relevant conflicts of interest to declare.

Lori Billinghurst: no relevant conflicts of interest to declare.

Kelly Russell: no relevant conflicts of interest to declare.

Ben Vandermeer: no relevant conflicts of interest to declare.

Tamara Durec: no relevant conflicts of interest to declare.

Ellen Crumley: no relevant conflicts of interest to declare.

Lisa Hartling: no relevant conflicts of interest to declare.

Terry Klassen: no relevant conflicts of interest to declare.

Meghan Linsdell: no relevant conflicts of interest to declare.

SOURCES OF SUPPORT

Internal sources

- Department of Pediatrics, University of Alberta, Canada
- Alberta Research Centre for Child Health Evidence, Canada

External sources

- Stollery Children's Hospital Foundation, Canada
- American Academy of Pediatrics Resident Research Grant, USA

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- At the recommendation of the Cochrane Pain, Palliative and Supportive Care Group, we narrowed the review criteria to include only placebo-controlled trials. We did not include studies with active comparators or standard of care as the control.
- The original protocol outlined a plan to address possible carry-over and period effects in studies of cross-over design. Given that migraine is an episodic disorder and that interventions were used to treat discrete migraine episodes, we considered the probability of there being carry-over and period effects to be very low. Thus, we deemed it inappropriate to exclude studies of cross-over design as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions*. We included all studies of cross-over design even if they did not report the time between treatment periods or a statistical test for carry-over effect. We performed a sensitivity analysis on study design to assess the influence of cross-over studies on measures of effect and harm.
- We changed the allowed ages from the range of 3 to 18 years to any age under 18. For the subgroup analysis, we defined age groups according to custom in these types of studies (i.e. children less than 12 years of age; adolescents 12 to 17 years), as these age groups represent distinct ages whereby treatment may differ. No minimum age was included, as the diagnosis of migraine using appropriate criteria will preclude diagnosis in the very young, in whom criteria are not met.
- All studies reported the treatment of a single attack. The original protocol outlined a plan to address studies that reported the treatment of multiple headache episodes, but it was not necessary to implement this. If required, we will apply this plan in future revisions of the study.
- We added 'pain-free' as the primary outcome measure, given that it is a recommended primary outcome measure (Tfelt-Hansen 2012), it is the most desirable outcome for patients, and most studies report it.
- We changed 'headache relief' from a primary to a secondary outcome measure.
- No studies reported ordinal outcomes, continuous outcomes, or group mean change scores. Thus, we did not implement these aspects of the protocol, but we will if required in future revisions of the review.
- We removed photophobia and phonophobia from secondary outcome measures as recommended by reviewers and often only inferred from behaviour.
- We removed patient preference for treatment as a secondary outcome measure.
- We did not include assessment time points beyond two hours post medication administration given the known relatively short duration of migraine in many children and adolescents.
- We included a primary outcome measure to assess harm (i.e. any adverse events), as per the updated version 5.1.0 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).
- We revised the search strategy to improve search terms and focus on pharmacological interventions.
- We did not include a high versus low methodological quality score based on the Jadad scale in the sensitivity analysis, as we used the 'Risk of bias' tables to assess methodological quality. We used allocation concealment as per the protocol, as it is one of the domains in the 'Risk of bias' assessment.
- We added the GRADE assessment of quality of evidence.
- The original protocol proposed calculating within-patient improvement scores whenever the required data were reported, but these were not available.
- We added reports in a peer-reviewed indexed journal to the sensitivity analysis.
- We did not identify or include any quasi-randomized studies in the review. Future revisions of the review would not benefit from their inclusion, so we removed this selection criterion as suggested by reviewers.
- We amended the title from "Drugs for treating acute migraine headaches in children and adolescents" to "Drugs for the acute treatment of migraine in children and adolescents" for clarity.

NOTES

This systematic review has not previously been published in full form. The data have been presented at the American Headache Society Annual Scientific meeting.

Assessed for updating in 2018

A full search was performed in February 2018 and after screening the results the authors did not identify any potentially relevant studies. At October 2018, this review has been stabilised following discussion with the authors and editors. New treatments for migraine are anticipated, and we will update the review if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.

Assessed for updating in 2020

At October 2020 we are not aware of any potentially relevant studies likely to change the conclusions, although this is an active area of research and new studies are expected in the next two to three years. Following discussion with the authors and editors, this review has now been stabilised and will be reassessed for updating in two years. If appropriate we will update the review sooner if new evidence likely to change the conclusions is published, or if standards change substantially which necessitates major revisions.

INDEX TERMS

Medical Subject Headings (MeSH)

Acetaminophen [therapeutic use]; Analgesics, Non-Narcotic [*therapeutic use]; Dihydroergotamine [therapeutic use]; Ibuprofen [therapeutic use]; Migraine Disorders [*drug therapy]; Serotonin Receptor Agonists [adverse effects] [*therapeutic use]; Time Factors; Tryptamines [*therapeutic use]

MeSH check words

Adolescent; Child; Humans