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Aspirin with or without an antiemetic for acute migraine headaches in adults (Review)

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Cochrane Database of Systematic Reviews 2013, Issue 4. Art. No.: CD008041.

DOI: [10.1002/14651858.CD008041.pub3](https://doi.org/10.1002/14651858.CD008041.pub3).

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Aspirin with or without an antiemetic for acute migraine headaches in adults (Review)

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[Intervention Review]

Aspirin with or without an antiemetic for acute migraine headaches in adults

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ABSTRACT

Background

This is an updated version of the original Cochrane review published in Issue 4, 2010 (Kirthi 2010). Migraine is a common, disabling condition and a burden for the individual, health services and society. Many sufferers choose not to, or are unable to, seek professional help and rely on over-the-counter analgesics. Co-therapy with an antiemetic should help to reduce nausea and vomiting commonly associated with migraine headaches.

Objectives

To determine the efficacy and tolerability of aspirin, alone or in combination with an antiemetic, compared to placebo and other active interventions in the treatment of acute migraine headaches in adults.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, the Oxford Pain Relief Database, ClinicalTrials.gov, and reference lists for studies through 10 March 2010 for the original review and to 31 January 2013 for the update.

Selection criteria

We included randomised, double-blind, placebo-controlled or active-controlled studies, or both, using aspirin to treat a migraine headache episode, with at least 10 participants per treatment arm.

Data collection and analysis

Two review authors independently assessed trial quality and extracted data. Numbers of participants achieving each outcome were used to calculate relative risk and numbers needed to treat (NNT) or harm (NNH) compared to placebo or other active treatment.

Main results

No new studies were found for this update. Thirteen studies (4222 participants) compared aspirin 900 mg or 1000 mg, alone or in combination with metoclopramide 10 mg, with placebo or other active comparators, mainly sumatriptan 50 mg or 100 mg. For all efficacy outcomes, all active treatments were superior to placebo, with NNTs of 8.1, 4.9 and 6.6 for 2-hour pain-free, 2-hour headache relief, and 24-hour headache relief with aspirin alone versus placebo, and 8.8, 3.3 and 6.2 with aspirin plus metoclopramide versus placebo. Sumatriptan 50 mg did not differ from aspirin alone for 2-hour pain-free and headache relief, while sumatriptan 100 mg was better than the combination of aspirin plus metoclopramide for 2-hour pain-free, but not headache relief; there were no data for 24-hour headache relief.

Adverse events were mostly mild and transient, occurring slightly more often with aspirin than placebo.

Additional metoclopramide significantly reduced nausea ($P < 0.00006$) and vomiting ($P = 0.002$) compared with aspirin alone.

Authors' conclusions

We found no new studies since the last version of this review. Aspirin 1000 mg is an effective treatment for acute migraine headaches, similar to sumatriptan 50 mg or 100 mg. Addition of metoclopramide 10 mg improves relief of nausea and vomiting. Adverse events were mainly mild and transient, and were slightly more common with aspirin than placebo, but less common than with sumatriptan 100 mg.

PLAIN LANGUAGE SUMMARY

Aspirin with or without an antiemetic for acute migraine headaches in adults

This is an updated version of the original Cochrane review published in Issue 4, 2010 (Kirthi 2010); no new studies were found. A single oral dose of 1000 mg of aspirin reduced pain from moderate or severe to none by two hours in approximately 1 in 4 people (24%) taking aspirin, compared with about 1 in 10 (11%) taking placebo. Pain was reduced from moderate or severe to no worse than mild pain by two hours in roughly 1 in 2 people (52%) taking aspirin compared with approximately 1 in 3 (32%) taking placebo. Of those who experienced effective headache relief at two hours, more had that relief sustained over 24 hours with aspirin than with placebo. Addition of 10 mg of the antiemetic metoclopramide substantially increased relief of nausea and vomiting compared with aspirin alone, but made little difference to pain.

Oral sumatriptan 100 mg was better than aspirin plus metoclopramide for pain-free response at two hours, but otherwise there were no major differences between aspirin with or without metoclopramide and sumatriptan 50 mg or 100 mg. Adverse events with short-term use were mostly mild and transient, occurring slightly more often with aspirin than placebo, and more often with sumatriptan 100 mg than with aspirin.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Aspirin 900 mg or 1000 mg compared with placebo for migraine headache

Patient or population: migraine headache - moderate or severe pain

Settings: community

Intervention: aspirin 900 mg or 1000 mg

Comparison: placebo

Outcomes	Probable out- come with intervention	Probable out- come with comparator	NNT or NNTH and/ or relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Pain-free at 2 h	240 in 1000	110 in 1000	NNT 8.1 (6.4 to 11)	6 studies, 2027 participants 357 events	Moderate ¹	Standard tablet and soluble formulations
Headache relief at 2 h	520 in 1000	320 in 1000	NNT 4.9 (4.1 to 6.2)	6 studies, 2027 participants 848 events	Moderate ¹	Standard tablet and soluble formulations
Sustained pain-free at 24 h	No data					
Sustained headache relief at 24 h	390 in 1000	240 in 1000	NNT 6.6 (4.9 to 10)	3 studies, 1142 participants 361 events	Moderate ¹	Standard tablet and soluble formulations
At least one AE	120 in 1000	90 in 1000	NNH 34 (18 to 340)	5 studies, 1892 participants 206 events	Low	Standard tablet and soluble formulations
Serious AE	Insufficient data					

GRADE Working Group grades of evidence

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

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

Low quality: 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 quality: We are very uncertain about the estimate.

1 - Quality of evidence downgraded from high because of threat from potential publication bias with modest effect size and numbers of events

BACKGROUND

This is an updated version of the original Cochrane review published in Issue 4, 2010 (Kirthi 2010).

Description of the condition

Migraine is a common, disabling headache disorder, with considerable social and economic impact (Hazard 2009). Recent surveys found a one year prevalence of 15% for adults in European countries (Stovner 2010) and 13% for all ages in the United States (US) (Victor 2010), 21% in Russia (Ayzenberg 2012) and 9% for adults in China (Yu 2012). Migraine is more prevalent in women than in men (by a factor of two to three), and in the age range 30 to 50 years.

The International Headache Society (IHS) classifies two major subtypes (IHS 2004). Migraine without aura is the most common subtype. It is characterised by attacks lasting 4 to 72 hours that are typically of moderate to severe pain intensity, unilateral, pulsating, aggravated by normal physical activity and associated with nausea or photophobia and phonophobia, or both. Migraine with aura is characterised by reversible focal neurological symptoms that develop over a period of 5 to 20 minutes and last for less than 60 minutes, followed by headache with the features of migraine without aura. In some cases the headache may lack migrainous features or be absent altogether (IHS 2004).

A recent large prevalence study in the US found that over half of migraineurs had severe impairment or required bed rest during attacks. Despite this high level of disability and a strong desire for successful treatment, only a proportion of migraine sufferers seek professional advice for the treatment of attacks. The majority were not taking any preventive medication, although one-third met guideline criteria for offering or considering it. Nearly all (98%) migraineurs used acute treatments for attacks, with 49% using over-the-counter (OTC) medication only, 20% using prescription medication, and 29% using both. OTC medication included aspirin, other non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol (acetaminophen) and paracetamol with caffeine (Bigal 2008; Diamond 2007; Lipton 2007). Similar findings have been reported from other large studies in France and Germany (Lucas 2006; Radtke 2009).

The significant impact of migraine with regard to pain, functional health and well-being is well documented (Buse 2011; Leonardi 2005; Vos 2012). A cross-sectional survey of eight European Union (EU) countries (representing 55% of the adult population) has estimated an annual direct and indirect cost of migraine per person of €1222, and a total annual cost for the EU of €111 billion for adults aged 18 to 65 years (Linde 2012). Costs are substantially greater for the minority with chronic migraine compared with episodic migraine; they also vary between countries, probably due to differences in available therapies and the way they are delivered, and structural differences in healthcare systems (Bloudek 2012). In the US, the average annual direct cost per person has been estimated at \$1757 for episodic migraine and \$7750 for chronic migraine (Munakata 2009). Whatever the exact direct and indirect costs are for each country, it is clear that migraine presents a significant economic burden. Successful treatment of acute migraine attacks not only benefits patients by reducing their disability and improving health-related quality of life, but also has the potential to reduce the need for healthcare resources and

increase economic productivity. Migraine is ranked in the top 10 disorders for global years lived with disability (Vos 2012).

Description of the intervention

Medicines derived from willow bark, which is rich in salicylate, have been used for centuries for treating pain, fever and inflammation. In the mid-19th century, chemists first synthesised acetylsalicylic acid, and by the end of the century, Bayer had patented and was selling the drug, which they called aspirin, around the world.

Aspirin is used to treat mild to moderate pain, including migraine headache pain; inflammatory conditions such as rheumatoid arthritis; and, in low doses, it is used as an antiplatelet agent in cardiovascular disease. It is a potent gastrointestinal irritant, and may cause discomfort, ulcers and bleeding. It may also cause tinnitus at high doses, and it is no longer used in children and adolescents, in whom it may cause Reye's syndrome (swelling of the brain that may lead to coma and death). Its use as an analgesic and antipyretic agent has declined, largely due to these adverse events, as newer products have become available. However, in some countries it may be the only drug readily available, and for some conditions, such as migraine, some individuals report it to be an effective and reliable treatment.

In order to establish whether aspirin is an effective analgesic at a specified dose in acute migraine attacks, it is necessary to study its effects in circumstances that permit detection of pain relief. Such studies are carried out in individuals with established pain of moderate to severe intensity, using single doses of the interventions. Participants who experience an inadequate response with either placebo or active treatment are permitted to use rescue medication, and the intervention is considered to have failed in those individuals. In clinical practice, however, individuals would not normally wait until pain is of at least moderate severity, and may take a second dose of medication if the first dose does not provide adequate relief. Once analgesic efficacy is established in studies using single doses in established pain, further studies may investigate different treatment strategies and patient preferences. These are likely to include treating the migraine attack early while pain is mild, and using a low dose initially, with a second dose if response is inadequate.

How the intervention might work

Aspirin irreversibly inhibits cyclo-oxygenase enzymes, which are needed for prostaglandin and thromboxane synthesis. Prostaglandins mediate a variety of physiological functions such as maintenance of the gastric mucosal barrier, regulation of renal blood flow, and regulation of endothelial tone. They also play an important role in mediating inflammatory and nociceptive processes. Suppression of prostaglandin synthesis is believed to underlie the analgesic effects of aspirin (Vane 1971).

The efficacy of oral medications is reduced in many migraineurs because of impaired gastrointestinal motility, which is associated with nausea, and because of non-absorption of the drug due to vomiting (Volans 1974). The addition of an antiemetic may improve outcomes by alleviating the often incapacitating symptoms of nausea and vomiting, and (at least potentially) by enhancing the bioavailability of the co-administered analgesic. In particular, prokinetic antiemetics such as metoclopramide, which stimulate gastric emptying, may improve outcomes by increasing absorption

of the analgesic (in this case, aspirin; [Ross-Lee 1983](#); [Volans 1975](#)). It has been claimed that treatment with metoclopramide alone can reduce pain in severe migraine attacks ([Colman 2004](#); [Salazar-Tortolero 2008](#)), but this claim requires further investigation because it is based on studies involving few participants, and metoclopramide has not been shown to be an analgesic in classical pain studies. The present review sought to determine whether treatment of acute migraine attacks with aspirin plus an antiemetic is in any way superior to treatment with aspirin alone.

Why it is important to do this review

Population surveys show that aspirin is frequently used to treat migraine headaches, but we could find no systematic review of the efficacy of this intervention in adults. It is important to know where this widely available and inexpensive drug fits in the range of therapeutic options for migraine therapy. For many migraineurs, non-prescription therapies offer convenience and may be the only therapies available or affordable. Aspirin is included in the World Health Organization (WHO) essential medicines list ([WHO 2011](#)).

This review is one of a series examining the efficacy of OTC treatments for migraine, including ibuprofen ([Rabbie 2013](#)), paracetamol (acetaminophen; [Derry 2013a](#)), and diclofenac ([Derry 2013b](#)), as well as oral sumatriptan ([Derry 2012b](#)), which is available without prescription in some countries.

OBJECTIVES

The objective of this review is to determine the efficacy and tolerability of aspirin, alone or in combination with an antiemetic, compared to placebo and other active interventions in the treatment of acute migraine headaches in adults.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised, double-blind, placebo-controlled or active-controlled studies using aspirin to treat a migraine headache episode. Studies had to have a minimum of 10 participants per treatment arm and report dichotomous data for at least one of the outcomes specified. We accepted studies reporting treatment of consecutive headache episodes if outcomes for the first, or each, episode were reported separately. We accepted cross-over studies if there was adequate (at least 24 hours) washout between treatments.

Types of participants

Studies included adults (at least 18 years of age) with migraine. We used the definition of migraine specified by the IHS ([IHS 1988](#); [IHS 2004](#)), although other definitions were considered if they conformed in general to IHS diagnostic criteria. There were no restrictions on migraine frequency, duration or type (with or without aura). We accepted studies that included participants taking stable prophylactic therapy to reduce the frequency of migraine attacks. If reported, details on any prophylactic therapy prescribed or allowed are provided in the [Characteristics of included studies](#) table.

Types of interventions

We included studies using a single dose of aspirin to treat a migraine headache episode when pain was of moderate to severe intensity, or investigated different dosing strategies or timing, or both, of the first dose in relation to headache intensity. There were no restrictions on dose or route of administration, provided the medication was self-administered.

Included studies could use either aspirin alone, or aspirin plus an antiemetic. The antiemetic had to be taken either combined with aspirin in a single formulation, or separately not more than 30 minutes before aspirin, and had to be self-administered.

A placebo comparator is essential to demonstrate that aspirin is effective in this condition. We considered active-controlled trials without a placebo as secondary evidence. We excluded studies designed to demonstrate prophylactic efficacy in reducing the number or frequency of migraine attacks.

Types of outcome measures

In selecting the main outcome measures for this review, we considered scientific rigour, availability of data and patient preferences ([Lipton 1999](#)). Patients with acute migraine headaches have rated complete pain relief, no headache recurrence, rapid onset of pain relief, and no side effects as the four most important outcomes ([Lipton 1999](#)).

In view of these patient preferences, and in line with the guidelines for controlled trials of drugs in migraine issued by the IHS ([IHS 2000](#)), the main outcomes to be considered were:

Primary outcomes

- Pain-free at two hours, without the use of rescue medication (PF2).
- Reduction in headache pain ('headache relief') at two hours (HR2) - pain reduced from moderate or severe to none or mild without the use of rescue medication.

Data for pain-free and headache relief at earlier time points were collected when reported and relevant, in this case because an effervescent formulation for early relief of headache pain was used in some studies.

Secondary outcomes

- Sustained pain-free during 24 hours (SPF24) - pain-free within two hours, with no use of rescue medication or recurrence of moderate to severe pain within 24 hours.
- Sustained pain reduction over 24 hours (SHR24) - headache relief at two hours, sustained for 24 hours, with no use of rescue medication or a second dose of study medication.
- Adverse events: participants with any adverse event during 24 hours postdose; serious adverse events; adverse events leading to withdrawal.

Pain intensity or pain relief had to be measured by the patient (not the investigator or care provider). Pain measures accepted for the primary outcomes were:

- Pain intensity (PI): 4-point categorical scale, with wording equivalent to none, mild, moderate and severe; or 100 mm visual analogue scale (VAS), where < 30 mm was considered equivalent

to mild or no pain and ≥ 30 mm equivalent to moderate or severe pain (Collins 1997);

- Pain relief (PR): 5-point categorical scale, with wording equivalent to none, a little, some, a lot, complete; or 100 mm VAS, where < 30 mm was considered equivalent to none or a little, and ≥ 30 mm equivalent to some, a lot or complete.

We considered only data obtained directly from the patient.

Other outcomes

In the earlier review we reviewed a number of other secondary outcomes:

- use of rescue medication.
- relief of headache-associated symptoms.
- relief of functional disability.

These are not now reported in detail in Results but have been moved to an Appendix (see 'Differences between the protocol and the review').

Definitions of important terms, including all measured outcomes, are provided in [Appendix 1](#).

Search methods for identification of studies

Electronic searches

The following databases were searched for the original review on 10 March 2010:

- the Cochrane Central Register of Controlled Trials (CENTRAL);
- MEDLINE (via Ovid);
- EMBASE (via Ovid);
- Oxford Pain Relief Database (Jadad 1996a).

For the update we searched:

- the Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 12, 2012);
- MEDLINE (via Ovid) from 1 January 2010 to 31 January 2013;
- EMBASE (via Ovid) from 1 January 2010 to 31 January 2013.

See [Appendix 2](#) for the search strategy for MEDLINE, [Appendix 3](#) for the search strategy for EMBASE, and [Appendix 4](#) for the search strategy for CENTRAL. There were no language restrictions.

Searching other resources

We searched reference lists of retrieved studies and review articles for additional studies, and for the update we searched www.Clinicaltrials.gov for information about both published and unpublished data, but no additional studies were identified. Grey literature and abstracts were not searched.

Data collection and analysis

Selection of studies

Two review authors independently carried out the searches and selected studies for inclusion. We viewed titles and abstracts of all studies identified by the electronic searches on screen, and excluded any that clearly did not satisfy inclusion criteria. We read full copies of the remaining studies to identify those suitable for

inclusion. Disagreements were settled by discussion with a third review author.

Data extraction and management

Two review authors independently extracted data from included studies using a standard data extraction form. Disagreements were settled by discussion with a third review author. One author entered data for the original review into RevMan 5.0, and one author entered information for the update (RevMan 2012).

Assessment of risk of bias in included studies

We used the Oxford Quality Score (Jadad 1996b) as the basis for inclusion, limiting inclusion to studies that were randomised and double-blind as a minimum. The scores for each study are reported in the [Characteristics of included studies](#) table.

Two authors independently assessed risk of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and adapted from those used by the Cochrane Pregnancy and Childbirth Group, with any disagreements resolved by discussion. We assessed the following for each study:

1. Random sequence generation (checking for possible selection bias). We assessed the method used to generate the allocation sequence as: low risk of bias (any truly random process, e.g. random number table; computer random number generator); unclear risk of bias (method used to generate sequence not clearly stated). Studies using a non-random process (e.g. odd or even date of birth; hospital or clinic record number) were excluded.
2. Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions before assignment determines whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We assessed the methods as: low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes); unclear risk of bias (method not clearly stated). Studies that did not conceal allocation (e.g. open list) were excluded.
3. Blinding of outcome assessment (checking for possible detection bias). We assessed the methods used to blind study participants and outcome assessors from knowledge of which intervention a participant received. We assessed the methods as: low risk of bias (study states that it was blinded and describes the method used to achieve blinding, e.g. identical tablets; matched in appearance and smell); unclear risk of bias (study states that it was blinded but does not provide an adequate description of how it was achieved). Studies that were not double-blind were excluded.
4. Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data). We assessed the methods used to deal with incomplete data as: low risk ($< 10\%$ of participants provided no data without acceptable reason - e.g. they were randomised but did not have a qualifying headache). Studies with high data loss were excluded.
5. Size of study (checking for possible biases confounded by small size). We assessed studies as being at low risk of bias (≥ 200 participants per treatment arm); unclear risk of bias (50 to 199 participants per treatment arm); high risk of bias (< 50 participants per treatment arm).

Measures of treatment effect

We used relative risk (or 'risk ratio', RR) to establish statistical difference. We used numbers needed to treat (NNT) and pooled percentages as absolute measures of benefit or harm.

We used the following terms to describe adverse outcomes in terms of harm or prevention of harm:

- When significantly fewer adverse outcomes occur with aspirin than with control (placebo or active) we use the term the number needed to treat to prevent one event (NNTp).
- When significantly more adverse outcomes occur with aspirin compared with control (placebo or active) we use the term the number needed to harm or cause one event (NNH).

Unit of analysis issues

The unit of analysis was the individual patient.

Dealing with missing data

The most likely source of missing data was in cross-over studies; we planned to use only first-period data where possible, but where that was not provided, we treated the results as if they were parallel group results. Where there were substantial missing data in any study, we would comment on this and perform sensitivity analyses to investigate their effect.

For all outcomes we carried out analyses, as far as possible, on a modified intention-to-treat basis, i.e. we included all participants who were randomised and received an intervention. Where sufficient information was reported, we re-included missing data in the analyses we undertook. We would exclude data from outcomes where results from $\geq 10\%$ of participants are missing with no acceptable reason provided or apparent.

Assessment of heterogeneity

We assessed heterogeneity of response rates using L'Abbé plots, a visual method for assessing differences in results of individual studies. (L'Abbé 1987). Where data could be pooled, we report the I^2 statistic.

Assessment of reporting biases

We assessed publication bias by examining the number of participants in trials with zero effect (relative risk of 1.0) needed for the point estimate of the NNT to increase beyond a clinically useful level (Moore 2008). In this case, we specified a clinically useful level as an NNT of ≥ 8 for pain-free at two hours, and NNT ≥ 6 for headache relief at two hours.

Data synthesis

We analysed studies using a single dose of aspirin in established pain of at least moderate intensity separately from studies in which medication was taken before pain was well established or in which a second dose of medication was permitted.

We calculated effect sizes and combined data for analysis only for comparisons and outcomes where there were at least two studies and 200 participants (Moore 1998). We calculated relative risk of benefit or harm with 95% confidence intervals (CIs) using a fixed-effect model (Morris 1995). We calculated NNT, NNTp and NNH with 95% CIs using the pooled number of events by the method of Cook

and Sackett (Cook 1995). A statistically significant difference from control is assumed when the 95% CI of the relative risk of benefit or harm did not include the number one.

We used the z test to determine significant differences between NNT, NNTp or NNH for different groups in subgroup and sensitivity analyses (Tramèr 1997).

We describe data from comparisons and outcomes with only one study or fewer than 200 participants in the text and summary tables where appropriate for information and comparison, but they are not analysed quantitatively.

Subgroup analysis and investigation of heterogeneity

Issues for potential subgroup analysis were dose, monotherapy versus combination with an antiemetic, formulation and route of administration. For combined treatment with an antiemetic, we planned to compare different antiemetics if there were sufficient data.

Sensitivity analysis

We planned sensitivity analysis for study quality (Oxford Quality Score of 2 versus 3 or more), and for migraine type (with aura versus without aura). A minimum of two studies and 200 participants had to be available for any sensitivity analysis.

RESULTS

Description of studies

Included studies

New searches in January 2013 did not identify any additional studies.

Thirteen studies fulfilled the inclusion criteria for this review (Boureau 1994; Chabriat 1994; Diener 2004a; Diener 2004b; Geraud 2002; Henry 1995; Lange 2000; Le Jeune 1998; Lipton 2005; MacGregor 2002; Tfelt-Hansen 1995; Thomson 1992; Titus 2001), with a total of 5261 treated migraine attacks (4222 participants) providing data. Boureau 1994; Diener 2004b; MacGregor 2002 together provided information on treatment of 1039 more migraine attacks than participants. Details of the included studies are provided in the [Characteristics of included studies](#) table.

All included studies recruited participants between 18 and 65 years of age (mean ages ranging from 37 to 44 years), meeting IHS criteria for migraine with or without aura (IHS 1988; IHS 2004). All participants had a history of migraine symptoms for at least 12 months, with between one and six attacks per month of moderate to severe intensity, prior to the study period. One study (Thomson 1992) excluded participants needing prophylactic treatment. Four studies specified that any prophylactic treatment had to have been stable for at least two (Boureau 1994) or three (Chabriat 1994; Le Jeune 1998; Lipton 2005) months before the study period, while the remainder did not mention prophylaxis.

Three studies excluded participants who vomited either at least 20% of the time during migraine attacks (Lange 2000; Lipton 2005) or during the majority of attacks (MacGregor 2002). Another study excluded participants whose migraine headaches were never accompanied by nausea or vomiting (Chabriat 1994). One study excluded data from migraine attacks with aura (Henry 1995), whilst

another study used only data from migraine attacks without aura that also featured all three symptoms of nausea, photophobia and phonophobia (Diener 2004a). Five studies excluded participants who also experienced other types of headache (Boureau 1994; Diener 2004b; Geraud 2002; Henry 1995; Titus 2001).

Five studies had only a placebo comparator (Chabriat 1994; Henry 1995; Lange 2000; Lipton 2005; MacGregor 2002), four had only an active comparator (Geraud 2002; Le Jeunne 1998; Thomson 1992; Titus 2001), and four had both placebo and active comparators (Boureau 1994; Diener 2004a; Diener 2004b; Tfelt-Hansen 1995).

All treatments were administered orally, and when the headache was of moderate or severe intensity, except in Boureau 1994, where up to 15% of participants had "slight" headache at baseline. No studies specifically investigated early treatment of attacks while pain intensity was still mild. Aspirin 1000 mg was given either as a tablet or an effervescent solution to 940 participants in five studies (Boureau 1994; Diener 2004a; Diener 2004b; Lange 2000; Lipton 2005). In one study, aspirin was given to 73 participants as a 900 mg mouth-dispersible dose (MacGregor 2002). In seven studies, aspirin equivalent to 900 mg was given either as the lysine salt, calcium carbasalate (a soluble complex of aspirin) or an effervescent solution, in combination with metoclopramide 10 mg, to 1186 participants (Chabriat 1994; Geraud 2002; Henry 1995; Le Jeunne 1998; Tfelt-Hansen 1995; Thomson 1992; Titus 2001). We did not identify any studies in which aspirin was combined with an antiemetic other than metoclopramide.

Sumatriptan 50 mg was given to 361 participants in two studies (Diener 2004a; Diener 2004b), and sumatriptan 100 mg to 294 participants in another two studies (Tfelt-Hansen 1995; Thomson 1992). Zolmitriptan 2.5 mg was given to 326 participants in one study (Geraud 2002). Four studies compared aspirin treatment with non-triptan medications: one gave acetaminophen 400 mg plus codeine 25 mg to 198 participants (Boureau 1994); one gave ibuprofen 400 mg to 212 participants (Diener 2004b); one gave ergotamine 1 mg plus 100 mg caffeine to 132 participants (Le Jeunne 1998); and the other gave ergotamine 2 mg plus caffeine 200 mg to 115 participants (Titus 2001). A total of 1424 participants received placebo.

Some studies were inconsistent in the denominators reported and, for instance, reported on one or two patients fewer than the intention-to-treat population for some outcomes, but not for others, without giving a reason. As the denominators were always within a few patients of the intention-to-treat population, we used the denominators given.

Three studies (Boureau 1994; Diener 2004b; MacGregor 2002) used a cross-over design in which participants treated consecutive

headaches with different study medications. Boureau 1994 did not specify a washout period between attacks, while Diener 2004b and MacGregor 2002 specified a minimum of 48 hours between qualifying attacks. The remaining studies used a parallel-group design, in which participants received only one type of medication. In five studies (Diener 2004a; Henry 1995; Lange 2000; Lipton 2005; Titus 2001) participants treated only one attack, while in the remaining five studies they treated more than one attack with the same medication. In Chabriat 1994, Le Jeunne 1998 and Tfelt-Hansen 1995 two attacks were treated, while in Geraud 2002 and Thomson 1992 three attacks were treated; some outcomes were reported for each attack separately, while for other outcomes attacks were combined. We have used data for the first attack only, where these data were reported separately, for efficacy outcomes to avoid problems of double counting participants and repeated measures for the same individuals; for use of rescue medication and adverse event data, we have accepted data from multiple attacks in the absence of first-attack data in order to be inclusive and provide conservative estimates. In Geraud 2002, a second dose of study medication was permitted if there was an inadequate response to the first; data for the first dose in the first attack were available for one primary outcome. In Titus 2001 one attack was treated with up to three doses of the same medication if an adequate response was not obtained; data for our primary outcomes were not available for the first dose only.

Excluded studies

Six studies were excluded after reading the full report (Chabriat 1993; Diener 2005; Limmroth 1999; Nebe 1995; Tfelt-Hansen 1980; Tfelt-Hansen 1984). Reasons for exclusion are provided in the [Characteristics of excluded studies](#) table.

Risk of bias in included studies

All studies were randomised and double-blind, and all reported on withdrawals and dropouts, thus minimising bias. Four scored 5 of 5 (Diener 2004a; Diener 2004b; Geraud 2002; Titus 2001), six scored 4 of 5 (Boureau 1994; Le Jeunne 1998; Lipton 2005; MacGregor 2002; Tfelt-Hansen 1995; Thomson 1992) and three scored 3 of 5 (Chabriat 1993; Henry 1995; Lange 2000) on the Oxford Quality Score. Points were lost because of failure to adequately describe the methods of randomisation and blinding. Details are provided in the [Characteristics of included studies](#) table.

A risk of bias table was completed for randomisation, allocation concealment, blinding, incomplete outcome data, and study size. No study described the method of allocation concealment, and only three (Diener 2004b; Geraud 2002; Lipton 2005) had more than 200 attacks per treatment arm, but none were at high risk of bias (Figure 1).

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies. **Effects of interventions**

See: [Summary of findings for the main comparison](#)

Aspirin doses of 900 mg and 1000 mg were considered sufficiently similar to combine for analysis. All included studies that provided data for analysis reported outcomes using the standard 4-point categorical pain intensity scale (none, mild, moderate, severe).

Details of outcomes in individual studies are provided in [Appendix 5](#) (efficacy) and [Appendix 6](#) (adverse events and withdrawals). Results for pain-free and headache relief responses are summarised in Summary of results A.

Pain-free at two hours**Aspirin 900 mg or 1000 mg versus placebo**

Six studies (2027 participants) provided data; three used a 1000 mg effervescent formulation of aspirin ([Diener 2004a](#); [Diener 2004b](#); [Lange 2000](#)), two used a 1000 mg oral tablet formulation ([Boureau 1994](#); [Lipton 2005](#)) and one used a 900 mg mouth-dispersible dose ([MacGregor 2002](#)).

- The proportion of participants pain-free at two hours with aspirin 1000 mg was 24% (240/1008; range 14% to 29%).
- The proportion of participants pain-free at two hours with placebo was 11% (117/1019; range 5% to 17%).
- The relative benefit of treatment compared with placebo was 2.1 (95% CI 1.7 to 2.6) ([Analysis 1.1](#); [Figure 2](#)); the NNT was 8.1 (6.4 to 11).

Figure 2. Forest plot of comparison: 1 Aspirin 900 mg or 1000 mg versus placebo, outcome: 1.1 Pain free at 2 hours. **Footnotes**

(1) aspirin 900 mg

Aspirin 900 mg plus metoclopramide 10 mg versus placebo

Two studies (519 participants) provided data for the 900 mg oral tablet formulation in combination with oral metoclopramide 10 mg versus placebo ([Henry 1995](#); [Tfelt-Hansen 1995](#)).

- The proportion of participants pain-free at two hours with aspirin 900 mg plus metoclopramide 10 mg was 18% (47/262; range 14% to 21%).

- The proportion of participants pain-free at two hours with placebo was 7% (17/257; range 5% to 8%).
- The relative benefit of treatment compared with placebo was 2.7 (1.6 to 4.6) ([Analysis 2.1](#)); the NNT was 8.8 (5.9 to 17).

Subgroup analysis comparing studies using aspirin alone and studies using aspirin plus metoclopramide gave $z = 0.3051$, $P = 0.76$.

There was no significant difference between treatments for this outcome.

A L'Abbé plot for this outcome shows a high degree of clinical homogeneity in these studies of aspirin $\pm$ metoclopramide versus placebo ([Figure 3](#)).

Figure 3. L'Abbé plot showing pain-free at 2 h response in individual studies. Each circle represents one study, with size on the inset scale.

Aspirin 1000 mg versus active comparator

Two studies (726 participants) compared effervescent aspirin 1000 mg with sumatriptan 50 mg ([Diener 2004a](#); [Diener 2004b](#)).

- The proportion of participants pain-free at two hours with aspirin 1000 mg was 26% (97/367).
- The proportion of participants pain-free at two hours with sumatriptan 50 mg was 32% (116/359).
- The relative benefit of aspirin compared with sumatriptan was 0.82 (0.65 to 1.03) ([Analysis 3.1](#)). There was no significant difference between treatments.

One study ([Boureau 1994](#)) compared 1000 mg aspirin (tablet) with paracetamol 400 mg plus codeine 25 mg, while another ([Diener 2004b](#)) compared 1000 mg aspirin (tablet) with ibuprofen 400 mg. For neither were there sufficient data for analysis ([Appendix 5](#)).

Aspirin 900 mg plus metoclopramide 10 mg versus active comparator

Two studies (528 participants) compared aspirin 900 mg (tablet or lysine equivalent) plus metoclopramide 10 mg with sumatriptan 100 mg ([Tfelt-Hansen 1995](#); [Thomson 1992](#)).

- The proportion of participants pain-free at two hours with aspirin 900 mg or 1000 mg plus metoclopramide 10 mg was 18% (48/273).
- The proportion of participants pain-free at two hours with sumatriptan 100 mg was 28% (71/255).
- The relative benefit of aspirin plus metoclopramide compared with sumatriptan was 0.63 (0.45 to 0.87) ([Analysis 4.1](#)); the NNT for sumatriptan compared with aspirin plus metoclopramide was 9.8 (5.8 to 32).

One study ([Le Jeunne 1998](#)) compared aspirin 900 mg (as calcium carbasalate) plus metoclopramide 10 mg with ergotamine 1 mg plus caffeine 100 mg (266 participants). There were insufficient data for analysis ([Appendix 5](#)).

Headache relief at two hours

Aspirin 900 or 1000 mg versus placebo

Six studies (2027 participants) in which individuals were treated with aspirin alone provided data. Three studies used an effervescent formulation ([Diener 2004a](#); [Diener 2004b](#); [Lange 2000](#)), whilst the other three studies used a mouth-dispersible ([MacGregor 2002](#)) or oral tablet formulation ([Boureau 1994](#); [Lipton 2005](#)).

- The proportion of participants experiencing headache relief at two hours with aspirin 900 mg or 1000 mg was 52% (525/1008; range 48% to 55%).
- The proportion of participants experiencing headache relief at two hours with placebo was 32% (323/1019; range 19% to 37%).
- The relative benefit of treatment compared with placebo was 1.6 (1.5 to 1.8) (Analysis 1.2; Figure 4); the NNT was 4.9 (4.1 to 6.2).

Figure 4. Forest plot of comparison: 1 Aspirin 900 mg or 1000 mg versus placebo, outcome: 1.2 Headache relief at 2 hours.

Footnotes

(1) aspirin 900 mg

Aspirin 900 mg plus metoclopramide 10 mg versus placebo

Three studies (765 participants) provided data. Two studies used a lysine equivalent formulation of aspirin (Chabriat 1994; Tfelt-Hansen 1995), whilst the other study used an effervescent formulation (Henry 1995).

- The proportion of participants experiencing headache relief at two hours with aspirin 900 mg plus metoclopramide 10 mg was 57% (219/386; range 54% to 59%).
- The proportion of participants experiencing headache relief at two hours with placebo was 26% (100/379; range 24% to 29%).

- The relative benefit of treatment compared with placebo was 2.2 (1.8 to 2.6) (Analysis 2.2); the NNT was 3.3 (2.7 to 4.2).

Subgroup analysis comparing studies using aspirin alone and studies using aspirin plus metoclopramide gave $z = 2.48$, $P = 0.0131$, showing that aspirin plus metoclopramide was significantly more effective than aspirin alone at achieving headache relief at two hours.

A L'Abbé plot for this outcome shows a high degree of clinical homogeneity in these studies of aspirin ± metoclopramide versus placebo (Figure 5).

Figure 5. L'Abbé plot showing headache response at 2 h in individual studies. Each circle represents one study, with size on the inset scale.

Aspirin 1000 mg versus active comparator

Two studies (726 participants) compared effervescent aspirin 1000 mg with sumatriptan 50 mg (Diener 2004a; Diener 2004b).

- The proportion of participants experiencing headache relief at two hours with aspirin 1000 mg was 51% (188/367).
- The proportion of participants experiencing headache relief at two hours with sumatriptan 50 mg was 53% (191/359).
- The relative benefit of aspirin compared with sumatriptan was 0.96 (0.84 to 1.1) (Analysis 3.2). There was no significant difference between treatments.

One study (Boureau 1994) compared 1000 mg aspirin (tablet) with paracetamol 400 mg plus codeine 25 mg, and another (Diener 2004b) compared 1000 mg aspirin (tablet) with ibuprofen 400 mg. In both cases there were insufficient data for analysis (Appendix 5).

Aspirin 900 mg plus metoclopramide 10 mg versus active comparator

Two studies (523 participants) compared aspirin 900 mg plus metoclopramide 10 mg with sumatriptan 100 mg (Tfelt-Hansen 1995; Thomson 1992). One used the lysine equivalent and the other a standard oral tablet.

- The proportion of participants experiencing headache relief at two hours with aspirin 900 mg plus metoclopramide 10 mg was 51% (138/271).
- The proportion of participants experiencing headache relief at two hours with sumatriptan 100 mg was 54% (137/252).

- The relative benefit of treatment compared with placebo was 0.93 (0.79 to 1.1) (Analysis 4.2). There was no significant difference between treatments.

One study each compared aspirin 900 mg plus metoclopramide 10 mg with zolmitriptan 25 mg (Geraud 2002) and ergotamine 1 mg plus caffeine 100 mg (Le Jeunne 1998). There were insufficient data for analysis with either comparator (Appendix 5). Titus 2001 compared aspirin 900 mg plus metoclopramide 10 mg with ergotamine 2 mg plus caffeine 200 mg, but reported no usable data.

Headache relief at one hour

Aspirin 900 or 1000 mg versus placebo

Four studies (1288 participants) comparing aspirin 900 mg or 1000 mg with placebo provided data. Two used an effervescent formulation (Diener 2004a; Diener 2004b), one a mouth dispersible formulation (MacGregor 2002) and one a tablet (Lipton 2005).

- The proportion of participants experiencing headache relief at one hour with aspirin 900 mg or 1000 mg was 33% (209/641; range 24% to 41%).
- The proportion of participants experiencing headache relief at one hour with placebo was 15% (99/647; range 11% to 21%).
- The relative benefit of treatment compared with placebo was 2.1 (1.7 to 2.6) (Analysis 1.3); the NNT was 5.8 (4.3 to 8.0).

Removing the study using the tablet formulation (Lipton 2005) did not significantly change the result (RR 2.3 (1.7 to 3.0); NNT 5.6 (3.4 to 5.4)).

Aspirin 1000 mg versus active comparator

Two studies (726 participants) comparing aspirin 1000 mg with sumatriptan 50 mg provided data ([Diener 2004a](#); [Diener 2004b](#)). Both used effervescent aspirin and oral sumatriptan.

- The proportion of participants experiencing headache relief at 1 hour with aspirin 1000 mg was 38% (138/367; range 34% to 42%).
- The proportion of participants experiencing headache relief at 1 hour with sumatriptan 50 mg was 24% (85/359; range 23% to 24%).
- The relative benefit of treatment compared with sumatriptan 50 mg was 1.6 (1.3 to 2.0) ([Analysis 3.3](#)); the NNT was 7.2 (4.9 to 14).

One study ([Diener 2004b](#)) compared effervescent aspirin 1000 mg with ibuprofen 400 mg (432 participants). There were insufficient data for analysis.

Aspirin plus metoclopramide versus placebo or versus active comparator

No studies using aspirin plus metoclopramide reported on headache relief at one hour.

Sustained pain-free at 24 hours

None of the studies provided data on the proportion of participants who were pain-free at two hours and remained pain-free for 24 hours.

Sustained headache relief at 24 hours

Aspirin 1000 mg versus placebo

Three studies (1142 participants) provided data for this outcome. Two used an effervescent formulation ([Diener 2004a](#); [Diener 2004b](#)) and one a tablet ([Lipton 2005](#)).

- The proportion of participants with 24-hour sustained relief with aspirin 1000 mg was 39% (223/568; range 33% to 42%).
- The proportion of participants with 24-hour sustained relief with placebo was 24% (138/574; range 22% to 25%).
- The relative benefit of treatment compared with placebo was 1.6 (1.4 to 2.0) ([Analysis 1.4](#)); the NNT was 6.6 (4.9 to 10).

Removing the study using the tablet formulation ([Lipton 2005](#)) did not significantly change the result (RR 1.6 (1.3 to 2.0); NNT 6.8 (4.7 to 12)).

Aspirin 900 mg plus metoclopramide 10 mg versus placebo

One study (257 participants) reported this outcome ([Tfelt-Hansen 1995](#)). Because there were more than 200 participants, for information and comparison the results are given in Summary of results A; there was a significant benefit over placebo. Subgroup analysis comparing studies using aspirin alone and studies using aspirin plus metoclopramide gave $z = 0.7789$, $P = 0.43$, indicating no benefit with metoclopramide for this outcome.

Summary of results A: Pain-free and headache relief

	Studies	Attacks treated	Treatment (%)	Placebo or comparator (%)	NNT/NNTP (95% CI)	P for difference
Pain-free at 2 hours						
Aspirin 900 or 1000 mg versus placebo	6	2027	24	11	8.1 (6.4 to 11)	$z = 0.3051$
Aspirin 900 mg plus metoclopramide 10 mg versus placebo	2	519	18	7	8.8 (5.9 to 17)	$P = 0.76$
Aspirin 1000 mg versus sumatriptan 50 mg	2	726	26	32	Not calculated	
Aspirin 900 mg + metoclopramide 10 mg versus sumatriptan 100 mg	2	528	18	28	9.8 (5.8 to 32)	
Headache relief at 2 hours						
Aspirin 900 or 1000 mg versus placebo	6	2027	52	32	4.9 (4.1 to 6.2)	$z = 2.4847$
Aspirin 900 mg plus metoclopramide 10 mg versus placebo	3	765	57	26	3.3 (2.7 to 4.2)	$P = 0.013$
Aspirin 1000 mg versus sumatriptan 50 mg	2	522	51	53	Not calculated	

Aspirin 900 mg + metoclopramide 10 mg versus sumatriptan 100 mg	2	523	51	54	Not calculated	
Headache relief at 1 hour						
Aspirin 900 or 1000 mg versus placebo	4	1288	33	15	5.8 (4.6 to 7.9)	
Aspirin 1000 mg versus sumatriptan 50 mg	2	726	38	24	7.2 (4.9 to 14)	
Sustained headache relief at 24 hours						
Aspirin 1000 mg versus placebo	3	1142	39	24	6.6 (4.9 to 10)	z = 0.7789
Aspirin 900 mg plus metoclopramide 10 mg versus placebo	1	257	37	17	Not calculated	P = 0.43

Subgroup analyses

Dose, route of administration and choice of antiemetic drug

No subgroup analysis was possible for dose, route of administration or choice of antiemetic drug, since all studies used aspirin 900 mg or 1000 mg, all medication was administered orally, and the only antiemetic used was metoclopramide 10 mg.

Formulation: soluble versus tablet

For both pain-free ([Analysis 1.5](#)) and headache relief at two hours ([Analysis 1.6](#)) with aspirin alone versus placebo, there was no difference between soluble formulations (effervescent and mouth soluble) and tablets. For headache relief at one hour ([Analysis 1.3](#)), removing the single study using the tablet formulation did not significantly change the result. There were insufficient data to investigate the effect of formulation for other outcomes.

Monotherapy versus combination with an antiemetic

Results for aspirin alone compared with aspirin plus antiemetic (metoclopramide) are dealt with in the main analysis above.

Sensitivity analyses

Sensitivity analysis according to methodological quality was not possible because all studies scored $\geq 3/5$ on the Oxford Quality Score. Because one study ([Boureau 1994](#)) had no information on washout we repeated the analyses without this study. Omitting it made no difference to the results.

Adverse events

For studies that treated more than one attack with a single medication, results for adverse events were usually presented for all treated attacks. These data have been included in the adverse event analyses in order to be more inclusive and conservative ([Appendix 6](#)).

Any adverse event

All studies reported on the number of participants experiencing any adverse events after treatment; however, one did not report data for each treatment group separately ([MacGregor 2002](#)). Most

studies appeared to collect data using spontaneous reports in diary cards. Studies did not specify whether adverse event data continued to be collected after any rescue medication was taken; it seems likely that they were. Treatments were generally described as well tolerated, with most adverse events being of mild or moderate severity and self-limiting.

Results for participants experiencing any adverse event are summarised in Summary of results B.

Five studies with 1892 participants provided data on the number of participants experiencing adverse events for aspirin 1000 mg versus placebo ([Boureau 1994](#); [Diener 2004a](#); [Diener 2004b](#); [Lange 2000](#); [Lipton 2005](#)), and two studies with 566 participants for aspirin 900 mg plus metoclopramide versus placebo ([Henry 1995](#); [Tfelt-Hansen 1995](#)). Overall, adverse events occurred in 14% (172/1230) of aspirin ($\pm$ metoclopramide)-treated participants, and in 11% (136/1228) of placebo-treated participants, giving an RR of 1.3 (1.02 to 1.6) ([Analysis 5.1](#)). The NNH was 34 (18 to 340).

Two studies (730 participants) provided data for aspirin 1000 mg versus sumatriptan 50 mg ([Diener 2004a](#); [Diener 2004b](#)); 15% (55/369) of aspirin-treated participants and 18% (64/361) of sumatriptan-treated participants experienced adverse events. There was no significant difference between the treatments. Two studies (617 participants) reported data for aspirin 900 mg plus metoclopramide 10 mg compared with sumatriptan 100 mg ([Tfelt-Hansen 1995](#); [Thomson 1992](#)); 24% (78/320) of aspirin-treated participants and 37% (111/297) of sumatriptan-treated participants experienced adverse events, giving an RR of 0.66 (0.52 to 0.84) ([Analysis 6.1](#)). The NNTp was 8.4 (5.3 to 21).

One study presented adverse events data for aspirin 1000 mg versus ibuprofen 400 mg ([Diener 2004b](#)), and another reported for aspirin 1000 mg versus acetaminophen 400 mg with codeine 25 mg ([Boureau 1994](#)). Two studies reported adverse event data for aspirin 900 mg plus metoclopramide 10 mg compared with ergotamine 1 mg plus caffeine 100 mg ([Le Jeunne 1998](#)), or ergotamine 2 mg plus caffeine 200 mg ([Titus 2001](#)). There were insufficient data for analysis of this outcome for these active comparators ([Appendix 6](#)).

Overall, single doses of aspirin, with or without metoclopramide, did not cause significantly more or fewer adverse events in these studies than did placebo or comparator treatments, with the

exception of sumatriptan 100 mg, where for every eight individuals treated with sumatriptan, one would experience adverse events who would not have done with aspirin plus metoclopramide.

Summary of results B: Number of participants with adverse events within 24 hours of taking study medication

More or no more adverse events with treatment than comparator	Studies	Participants	Aspirin (%)	Comparator (%)	Relative risk (95% CI)	NNH (95% CI)
Aspirin ± metoclopramide versus placebo	7	2458	14	11	1.3 (1.02 to 1.6)	34 (18 to 340)
Aspirin 1000 mg versus placebo	5	1892	12	9	1.3 (1.00 to 1.7)	Not calculated
Aspirin 900 mg with metoclopramide 10 mg versus placebo	2	566	19	17	1.2 (0.82 to 1.7)	Not calculated
Fewer adverse events with treatment than comparator	Studies	Participants	Aspirin (%)	Comparator (%)	Relative risk (95% CI)	NN _{Tp} (95% CI)
Aspirin 1000 mg versus sumatriptan 50 mg	2	730	15	18	0.85 (0.61 to 1.2)	Not calculated
Aspirin 900 mg plus metoclopramide 10 mg versus sumatriptan 100 mg	2	642	24	36	0.66 (0.52 to 0.84)	8.4 (5.3 to 21)

Specific adverse events

Detailed adverse event reporting was inconsistent. Some studies did not report any details of individual adverse events; others reported all adverse events for each treatment group; while others reported those occurring in, say, $\geq 2\%$ of participants, or reported events for a specific body system. The body systems most frequently affected were the digestive system and nervous system. Individual studies were underpowered to detect differences between treatment groups, and inconsistent reporting prevented pooling of data (Appendix 6).

Serious adverse events

Serious adverse events were uncommon and were reported in only five studies. In one study a case of phlebitis following use of aspirin plus metoclopramide was considered to be drug-related, whilst another four events with aspirin plus metoclopramide and six with zolmitriptan were considered unrelated (Geraud 2002). In another study renal colic was reported in one participant after treating a migraine attack with aspirin, with no suspected causal relationship, but a perforated duodenal ulcer following use of ibuprofen was thought to be drug-related (Diener 2004b). In Lipton 2005, one participant had a perforated appendix following placebo treatment, and no causal relationship to the study medication was suspected. Acute atrial fibrillation requiring hospital admission was reported in one participant, and prolonged palpitations in another, after treatment with sumatriptan 100 mg (Tfelt-Hansen 1995). MacGregor 2002 reported two serious adverse events, considered unrelated to study medication: headache following treatment with aspirin and endometriosis following placebo. It is possible that these events were "severe" rather than "serious" (Appendix 6).

Three studies that provided data for adverse events did not explicitly state whether any serious adverse events had occurred (Boureau 1994; Diener 2004a; Henry 1995).

Withdrawals

Withdrawals due to adverse events were reported in six studies (Appendix 6). Geraud 2002 reported five withdrawals following aspirin plus metoclopramide (diarrhoea, palpitations plus asthenia, anxiety plus dry mouth, phlebitis) and three following zolmitriptan (dizziness, somnolence, vasodilation). MacGregor 2002 reported four withdrawals following aspirin (nausea, tinnitus, coughing, taste perversion) and none with placebo. Le Jeunne 1998 reported one withdrawal due to pulmonary embolism following aspirin plus metoclopramide, and one due to back pain following placebo. Tfelt-Hansen 1995 reported one withdrawal following aspirin plus metoclopramide, four following sumatriptan, and one following placebo, with no details given. Thomson 1992 reported no withdrawals following aspirin, and five following sumatriptan (headache, faintness and vomiting; scalp tingling, heaviness in the chest, globus and prolonged aura; stomach pain; dyspnoea and heaviness; worsened headache and nausea). Titus 2001 reported one participant treated with aspirin plus metoclopramide who withdrew because of sinusitis.

Withdrawals for other reasons and exclusions for protocol violations or missing data were generally well reported, although it was not always clear whether they occurred before or after taking rescue medication. The numbers of withdrawals were not likely to affect estimates of efficacy or harm. No statistical analysis of withdrawals was carried out.

DISCUSSION

Summary of main results

This review included 13 randomised, double-blind, controlled studies, with 4222 participants treating 5261 migraine headaches of moderate to severe intensity with either aspirin alone or aspirin plus metoclopramide. Nine of the studies were placebo-controlled; eight included an active comparator (sumatriptan, zolmitriptan, ibuprofen, paracetamol plus codeine, and ergotamine plus caffeine). No new studies were identified in searches carried out for the update in January 2013.

For the IHS preferred outcome of pain-free at two hours, both aspirin 900 mg or 1000 mg alone and aspirin 900 mg plus metoclopramide 10 mg were better than placebo, with NNTs of 8 to 9, and with no significant difference between active treatments. Only around one in four or one in five individuals treated with aspirin achieved this outcome. Sumatriptan 100 mg was significantly better than aspirin plus metoclopramide for this outcome (NNT = 10), but sumatriptan 50 mg was not different from aspirin alone. For headache relief at two hours, aspirin plus metoclopramide was significantly better than aspirin alone, with NNTs versus placebo of 3.3 and 4.9, respectively ($P = 0.013$). Around half of individuals treated achieved this outcome. There were no differences between aspirin alone and sumatriptan 50 mg, or aspirin plus metoclopramide and sumatriptan 100 mg. Headache relief at one hour with aspirin alone versus placebo was not significantly different from headache relief at two hours (NNTs of 5.8 (4.6 to 7.9) and 4.9 (4.1 to 6.2), respectively). For sustained headache relief at 24 hours, aspirin alone was better than placebo (NNT = 6.6), as was the combination of aspirin plus metoclopramide (NNT = 6.2).

Using a more soluble formulation of aspirin did not appear to give a substantial benefit over standard tablets for any of the primary outcomes. One would expect that a soluble formulation would be more rapidly absorbed and provide more rapid relief, but this effect (if present) might be missed if the first assessments are not made until one or two hours after dosing. In some circumstances, early, rapid pain relief is accompanied by better overall pain relief, but there was no indication of this in these studies.

Overall, slightly more participants experienced adverse events with either aspirin alone or aspirin plus metoclopramide than with placebo, but the difference barely reached statistical significance. There were slightly more participants experiencing adverse events with sumatriptan than with aspirin, but the difference was statistically significant only for sumatriptan 100 mg versus aspirin plus metoclopramide (NNH = 8.4). Most adverse events were described as mild or moderate, and transient; the digestive and nervous systems were most commonly affected. There were few serious adverse events, and most were not thought to be causally related to study medication, although one event of phlebitis was attributed to aspirin.

There were very limited data for aspirin with or without metoclopramide compared with other active comparators; there was no evidence for substantial differences between these interventions and aspirin for the main efficacy outcomes in these studies. We did not include in this review studies where aspirin was used in combination with another analgesic.

Additional analyses ([Appendix 7](#)) show that fewer participants treated with either aspirin alone or aspirin plus metoclopramide than with placebo needed rescue medication (NNTP = 4.8). There was no difference for aspirin alone versus sumatriptan 50 mg for this outcome, but for aspirin plus metoclopramide versus sumatriptan 100 mg, the difference just reached statistical significance in favour of sumatriptan 100 mg (NNH = 11).

Both aspirin alone and aspirin plus metoclopramide were better than placebo for alleviation of headache-associated symptoms, although there were too few vomiting events for reliable analysis, and no data for photophobia and phonophobia following aspirin plus metoclopramide. The combination therapy was significantly better than aspirin alone for relief of nausea ($P < 0.00006$) and vomiting ($P = 0.002$, but based on few data), as might be expected for an antiemetic.

Overall completeness and applicability of evidence

Included participants all had a diagnosis of migraine according to IHS criteria, with attacks occurring at a frequency of one to six per month and of moderate to severe intensity. Studies did not specifically recruit participants who usually used OTC medications, although [Lipton 2005](#) excluded those previously unresponsive to them. Participants requiring prophylaxis were either excluded or were able to continue with stable prophylaxis. The population studied is therefore not likely to be greatly biased towards milder or OTC-responsive individuals, or likely to exclude those with particularly difficult-to-treat headaches. Overall, there may be over-selection of individuals with more severe or difficult headaches than the general population since participants were recruited through headache clinics. Those with very frequent migraine attacks would be excluded, and this could include those whose headaches were regularly initially relieved, but then returned.

Generally the studies reported on most of the outcomes we considered important ([Lipton 1999](#); [IHS 2000](#)), although some presented data in ways that prevented pooling (for example, no first-attack data, but rather the sum, mean or range for ≥ 2 attacks). In general, the amount of missing data was small and unlikely to affect the results.

The amount of information for active comparators was small, so that even for sumatriptan conclusions about relative efficacy and harm must be cautious.

Individual studies are underpowered to determine differences between treatments for adverse events, and even pooling studies may not provide adequate numbers of events to demonstrate differences or allow confidence in the size of the effect. Single-dose studies are certainly unlikely to reveal rare, but potentially serious, adverse events. In these studies the number of participants experiencing any adverse event was probably a little higher with aspirin than with placebo, although these results may be confounded by recording of adverse events after taking rescue medication (which may disproportionately increase rates in the placebo group), and probably a little higher with larger doses of sumatriptan than with aspirin.

In the studies reviewed, participants with any contraindication to a study medication were excluded, so that the populations studied may differ from the general public who choose to self-

medicate with OTC aspirin. In addition, some studies used buffered formulations of aspirin that may cause less irritation in the stomach than standard OTC aspirin.

We found no studies specifically investigating the early use of aspirin, alone or in combination with an antiemetic, while headache intensity was still mild. In clinical practice most migraine sufferers do not wait until the headache becomes moderate or severe, and there is some evidence from studies with triptans that treating early, or when pain intensity is still mild, is better (Gendolla 2008).

Quality of the evidence

Included studies were of good methodological quality and validity. None adequately described the method of allocation concealment, but this may reflect the limitation of space in published articles rather than any flaw in methodology. Migraine was diagnosed using standard, validated criteria, and outcomes measured were generally those recommended by the IHS as being of clinical relevance, although not all studies reported all the outcomes we sought.

Single-dose studies of a medication, or studies examining a single dose taken a few times, do not capture all adverse events that may occur with longer term use. While short-term use of aspirin probably does not pose a large problem (Steiner 2009), the potential for gastrointestinal harm with long-term use is well documented (Derry 2000).

Potential biases in the review process

The main area for concern is the small numbers of actual events used to calculate some results combined with the modest effect size of aspirin (Moore 1998).

In the five studies treating more than one attack with the same intervention (Chabriot 1994; Geraud 2002; Le Jeunne 1998; Tfelt-Hansen 1995; Thomson 1992) we have used only data from the first attack for the primary outcomes. For cross-over studies we have used data from each phase, which may introduce unknown biases (Elbourne 2002).

There were substantial amounts of information in comparisons of aspirin alone compared to placebo for the primary outcomes of pain-free and headache relief at two hours. We consider that NNTs of 8 for the outcome pain-free at two hours (13% benefit over comparator), and 6 for headache relief at two hours (17% benefit over comparator), are working limits of clinical utility in this condition. For pain-free at two hours aspirin is already on the limit of utility, so even a small body of unidentified evidence showing no effect would affect interpretation of the results for this outcome. For headache relief at two hours we calculate that there would need to be at least 455 participants in unidentified studies showing no effect of aspirin over placebo to increase the NNT to the limit of utility (Moore 2008). We feel that it is unlikely this amount of null data exists.

Agreements and disagreements with other studies or reviews

This review is in broad agreement with earlier reviews comparing aspirin with placebo for acute migraine headaches (Diener 2006;

Lampl 2007; Oldman 2002), but includes more studies. Other reviews comparing aspirin with triptans also agree that aspirin has similar efficacy to oral sumatriptan (Mett 2008; Tfelt-Hansen 2008). Our findings are consistent with guidelines from the European Federation of Neurological Societies on drug treatment of acute migraine headaches (Evers 2009) and a summary of evidence-based recommendations for self-medication of migraine (Haag 2011).

A review of adverse events associated with single doses of aspirin in trials for migraine or tension-type headache or postoperative dental pain suggests that any small increases in gastrointestinal adverse events compared with placebo are not great enough to drive choice of drug therapy (Steiner 2009). We also found a small increase in mostly mild and transient adverse events with aspirin, suggesting good tolerability among the participants recruited into these studies.

AUTHORS' CONCLUSIONS

Implications for practice

Since the last version of this review no new studies were found. Aspirin 900 mg or 1000 mg is an effective treatment for some individuals with acute migraine headaches. Participants in these studies who responded to treatment experienced a reduction in both pain and associated symptoms, such as nausea and photophobia. The addition of 10 mg metoclopramide may provide additional pain relief and greater reduction in associated symptoms, particularly nausea. There was a small increase in the number of adverse events compared to placebo, but most events were mild and transient. Oral sumatriptan 50 mg or 100 mg provided similar efficacy in these studies (although sumatriptan 100 mg was superior to the aspirin plus metoclopramide combination for pain-free at two hours), but with slightly increased adverse events for sumatriptan 100 mg. Aspirin plus metoclopramide would seem to be a good first-line therapy for acute migraine attacks in this population, although frequent use over the longer-term may bring a higher risk of harm. Those who do not experience adequate relief should try an alternative therapy.

Implications for research

Studies directly comparing aspirin with paracetamol (which has a different mode of action), and with other triptans and NSAIDs would help to clarify the relative efficacy of the various treatment options. Ideally these studies would be head-to-head comparisons and would include a placebo comparator for internal validity.

ACKNOWLEDGEMENTS

Henry McQuay was an author on the original review.

We received financial support for the original review from the NHS Cochrane Collaboration Programme Grant Scheme and NIHR Biomedical Research Centre Programme. *Lifting The Burden*: the Global Campaign against Headache provided support for the editorial process.

Institution support for this update was from the Oxford Pain Research Trust, with editorial support funded by the International Headache Society.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Boureau 1994

Methods	Multicentre, randomised, double-blind, placebo-controlled, double-dummy, three-period, cross-over. Single oral dose of each treatment for each of three migraine attacks
	Assessments at 0 and 2 hours
	If pain not controlled, participants asked to wait 2 hours before taking rescue medication

Boureau 1994 (Continued)

Participants	<p>Aged 18-65 years, meeting IHS criteria for migraine without aura. At least 12-month history of migraine, with age of onset before 50 years and two to six attacks per month. Prophylaxis permitted if stable for $\geq$ 2 months</p> <p>Excluded participants with other types of headache. Included participants with 'slight' migraine at baseline, but reported primary outcomes for those with $\geq$ moderate pain separately</p> <p>N = 247 (198 treated three attacks and analysed for efficacy)</p> <p>M = 57, F = 190</p> <p>Mean age = 40 years</p> <p>36.8% of randomised participants were taking prophylactic therapy</p>
Interventions	<p>Aspirin 1000 mg, n = 198</p> <p>Acetaminophen 400 mg plus codeine 25 mg, n = 198</p> <p>Placebo, n = 198</p>
Outcomes	<p>Headache relief at 2 hours</p> <p>Pain-free at 2 hours</p> <p>PI: 100 mm VAS</p> <p>Mean PID at 2 hours (from baseline)</p> <p>Relief of nausea and vomiting</p> <p>Use of rescue medication</p> <p>Patient preference for medication</p> <p>Adverse events</p>
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-dummy design
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Completer analysis (participants treating all three attacks), but adequate reasons for exclusion given for all others
Study size	Unclear risk	50 to 200 participants per treatment group

Chabriat 1994

Methods	<p>Multicentre, randomised, double-blind, placebo-controlled, parallel-group. Single oral dose per attack. Participants treated two migraine attacks</p> <p>Medication taken when migraine headache pain of moderate or severe intensity</p> <p>Assessments at 0 and 2 hours</p> <p>If pain not controlled, participants asked to wait 2 hours before taking rescue medication</p>
Participants	<p>Aged 18-65 years, meeting IHS criteria for migraine with or without aura. At least 12-month history of migraine, with two to six attacks per month for three months prior to inclusion in study Prophylaxis permitted if stable for ≥ 3 months</p> <p>Excluded participants whose migraine headache was never accompanied by nausea or vomiting</p> <p>N = 266 (250 analysed for efficacy, 16 did not take medication)</p> <p>M = 46, F = 220</p> <p>Mean age 37 years</p>
Interventions	<p>Lysine acetylsalicylate 1650 mg (equivalent to 900 mg aspirin) plus metoclopramide 10 mg, n = 126</p> <p>Placebo, n = 124</p>
Outcomes	<p>Headache relief at 2 hours</p> <p>Pain-free at 2 hours</p> <p>PI: 4-point scale</p> <p>Presence of nausea and vomiting</p> <p>Headache recurrence at 24 hours</p> <p>PGE: 4-point scale</p> <p>Use of rescue medications</p>
Notes	Oxford Quality Score: R1, DB1, W1. Total = 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs described
Study size	Unclear risk	50 to 200 participants per treatment group

Diener 2004a

Methods	<p>Multicentre, randomised, double-blind, three-arm, parallel-group, double-dummy. Single oral dose</p> <p>Medication taken when migraine headache pain of moderate or severe intensity</p> <p>Assessments at 0, 0.5, 1, 1.5, 2 and 24 hours</p> <p>If pain not controlled, participants asked to wait 2 hours before taking rescue medication</p>
Participants	<p>Aged 18-65 years, meeting IHS criteria for migraine with and without aura. At least 12-month history of migraine, with one to six attacks per month</p> <p>N = 433</p> <p>M = 66, F = 367</p> <p>Mean age 42 years</p>
Interventions	<p>Effervescent acetylsalicylic acid 1000 mg, n = 146</p> <p>Sumatriptan 50 mg, n = 135</p> <p>Placebo, n = 152</p>
Outcomes	<p>Headache relief at 1 and 2 hours</p> <p>Pain-free at 2 hours</p> <p>24-hour sustained relief</p> <p>Adverse events</p> <p>Remission of associated symptoms: nausea, photophobia, phonophobia</p> <p>Overall impression of study medication</p> <p>Need for rescue medication</p>
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated randomisation list"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"Matching effervescent or tablet placebo"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Drop-outs described
Study size	Unclear risk	50 to 200 participants per treatment group

Diener 2004b

Methods	<p>Multicentre, randomised, double-blind, placebo-controlled, three-fold cross-over, double-dummy. Single oral dose per attack. Each participant treated three migraine attacks with different treatments.</p> <p>Medication taken when migraine headache pain of moderate or severe intensity</p> <p>Assessments at 0, 0.5, 1, 1.5, 2 and 24 hours</p> <p>If pain not controlled, participants encouraged to wait 2 hours before taking rescue medication</p> <p>Participants instructed to leave a minimum of 48 hours between consecutive study treatments to ensure that new attack and not migraine recurrence was being treated</p>
Participants	<p>Aged 18-65 years, meeting IHS criteria for migraine with and without aura. At least 12-month history of migraine, with one to six attacks per month</p> <p>N = 312</p> <p>M = 59, F = 253</p> <p>Mean age 38 years</p>
Interventions	<p>Effervescent acetylsalicylic acid 1000 mg, n = 222</p> <p>Ibuprofen 400 mg, n = 212</p> <p>Sumatriptan 50 mg, n = 226</p> <p>Placebo, n = 222</p>
Outcomes	<p>Pain intensity at 0.5, 1, 1.5 and 2 hours</p> <p>Nausea, vomiting, photophobia and phonophobia at same time points</p> <p>Global assessment of medication on 4-point categorical scale</p> <p>Use of 'escape medication'</p> <p>Time when headache disappeared</p> <p>Recurrence within 24 hours</p> <p>Adverse events</p>
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Treatment was assigned by a predetermined randomisation code"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double dummy design

Diener 2004b (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs described
Study size	Low risk	> 200 participants per treatment group

Geraud 2002

Methods	<p>Multicentre, randomised, double-blind, parallel-group, double-dummy. Single oral dose. Each participant treated three migraine attacks.</p> <p>Medication taken when migraine headache pain of moderate or severe intensity, provided it was within 6 hours of headache onset, and participants had been free from any previous migraine attack for at least 24 hours</p> <p>Assessments at 0 and 2 hours</p> <p>If pain not controlled, participants encouraged to wait 2 hours before taking rescue medication</p> <p>Patients returned to study centre after treating first attack, and were then given medication and diary cards for treating two further attacks</p>
Participants	<p>Aged 18-65 years, meeting IHS criteria for migraine with and without aura. At least 12-month history of migraine, with age of onset before 50 years and one to six attacks per month of moderate to severe intensity, for three months prior to inclusion in study</p> <p>Excluded participants with basilar, ophthalmoplegic or hemiplegic migraine, and those with non-migraine headache on more than 10 days per month for preceding 6 months</p> <p>Approximately half of participants in each treatment arm had previously been treated with acetylsalicylic acid plus metoclopramide, with 'good' or 'fair' response reported in roughly 55% of participants in each group</p> <p>Approximately 80% of participants had previously received or were currently receiving acetylsalicylic acid or NSAIDs alone, with 'good' or 'fair' response reported in approximately 45% of participants in both groups</p> <p>N = 666</p> <p>M = 100, F = 566</p> <p>Mean age 41 years</p>
Interventions	<p>Acetylsalicylic acid 900 mg plus metoclopramide 10 mg, n = 340</p> <p>Zolmitriptan 2.5 mg, n = 326</p>
Outcomes	<p>Headache response at 2 hours in all three attacks</p> <p>Pain-free at 2 hours after first dose in all three attacks</p> <p>Relief of migraine-associated symptoms (nausea, vomiting, photophobia, phonophobia)</p> <p>PI: standard 4-point scale</p> <p>Use of escape medication</p> <p>Headache recurrence</p> <p>Adverse events</p>

Geraud 2002 (Continued)

PGE: standard 4-point scale

Time to onset of meaningful migraine relief

Notes Oxford Quality Scale: R2, DB2, W1. Total = 5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated randomisation list"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-dummy design
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs described
Study size	Low risk	> 200 participants per treatment group

Henry 1995

Methods	Multicentre, randomised, double-blind, parallel-group. Single oral dose Medication taken when migraine headache pain was of moderate or severe intensity Assessments at 0, 2 and 24 hours
Participants	Aged 18 to 65 years, meeting IHS criteria for migraine Excluded attacks of migraine with aura. Excluded participants with tension headache N = 303 M = 35, F = 268 Mean age = 40 years
Interventions	Effervescent aspirin 900 mg plus metoclopramide 10 mg, n = 152 Placebo, n = 151
Outcomes	Headache relief at 2 hours Pain-free at 2 hours 24-hour sustained relief Use of rescue medication Relief of associated symptoms Functional disability

Henry 1995 (Continued)

PGE

Adverse events

Notes	Oxford Quality Score: R1, DB1, W1. Total = 3
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomised after drawing lots"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Drop-outs described, but 16% (aspirin) and 13% (placebo) not included in 2 h efficacy analyses because they were asleep
Study size	Unclear risk	50 to 200 participants per treatment group

Lange 2000

Methods	<p>Multicentre, randomised, double-blind, placebo-controlled, parallel-group. Single oral dose</p> <p>Participants instructed to take medication only if attack of at least moderate intensity, and within 6 hours of onset of symptoms</p> <p>Assessments at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6 and 24 hours</p> <p>If pain not controlled, participants asked to wait 2 hours before taking rescue medication</p>
Participants	<p>Aged 18-65 years, meeting IHS criteria for migraine. At least 12-month history of migraine, with one to six attacks per month</p> <p>Excluded participants usually so incapacitated as to require bed rest during attacks, and those who vomited more than 20% of time during attacks</p> <p>N = 374 (343 analysed for efficacy, 31 did not take medication)</p> <p>M = 62, F = 312</p> <p>Mean age = 42 years</p>
Interventions	<p>Effervescent acetylsalicylic acid 2 x 500 mg, n = 169</p> <p>Placebo, n = 174</p>
Outcomes	<p>Headache relief at 2 hours</p> <p>Pain-free after 2 hours</p> <p>Relief of migraine-associated symptoms: nausea, vomiting, photophobia, phonophobia (4-point scale)</p>

Lange 2000 (Continued)

PI : 4-point scale

PGE: 4-point scale

Headache recurrence within 24 hours

Use of rescue medication

Adverse events

Notes Oxford Quality Score: R1, DB1, W1. Total = 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs described
Study size	Unclear risk	50 to 200 participants per treatment group

Le Jeune 1998

Methods	<p>Multicentre, randomised, double-blind, double-dummy, parallel-group. Single oral dose</p> <p>Each participant to treat two attacks, as soon as intensity was moderate or severe</p> <p>Assessments at 0, 2 and 24 hours</p> <p>If pain not controlled, participants encouraged to wait 2 hours before taking rescue medication</p>
Participants	<p>Aged 18-65 years, meeting IHS criteria for migraine with and without aura. At least 12-month history of migraine, with one to six attacks moderate or severe attacks per month. Prophylaxis permitted if stable for ≥ 3 months</p> <p>N = 296 randomised (268 took study medication)</p> <p>M = 47, F = 249</p> <p>Mean age 37 years</p>
Interventions	<p>Calcium carbasalate 1145 mg (equivalent to 900 mg aspirin) plus metoclopramide 10 mg, n = 136</p> <p>Ergotamine 1 mg plus metoclopramide 10 mg, n = 132</p>
Outcomes	<p>Headache relief at 2 hours</p> <p>Pain-free after 2 hours</p>

Le Jeunne 1998 (Continued)

Relief of nausea

PGE: 4-point scale

Headache recurrence within 24 hours

Use of rescue medication

Adverse events

Notes Oxford Quality Score: R1, DB2, W1. Total = 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Predetermined randomisation list
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-dummy method, using tablet and sachet
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs described
Study size	Unclear risk	50 to 200 participants per treatment group

Lipton 2005

Methods	<p>Multicentre, randomised, double-blind, placebo-controlled, parallel-group. Single oral dose</p> <p>Medication administered when migraine headache pain of moderate or severe intensity</p> <p>Assessments at 0, 0.5, 1, 2, 3, 4, 5, 6 and 24 hours</p> <p>If pain not controlled, participants asked to wait 2 hours before taking rescue medication</p>
Participants	<p>Aged 18-50 years, meeting IHS criteria for migraine with and without aura. At least 12-month history of migraine, with one to six attacks per month of at least moderate pain intensity. Prophylaxis permitted if stable for ≥ 3 months</p> <p>N = 409 (401 with confirmed migraine)</p> <p>M = 85, F = 316</p> <p>Mean age 38 years</p>
Interventions	<p>Aspirin 1000 mg, n = 205</p> <p>Placebo, n = 204</p>
Outcomes	<p>Headache relief at 1 and 2 hours</p> <p>Pain-free at 2 hours</p>

Lipton 2005 (Continued)

24 hour sustained relief

Adverse events

Relief of associated symptoms: nausea, photophobia, phonophobia

Need for rescue medication

PI: standard 4-point scale

Notes Oxford Quality Score: R1, DB2, W1. Total = 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"Matched placebo"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs described
Study size	Low risk	> 200 participants per treatment group

MacGregor 2002

Methods	<p>Multicentre, randomised, double-blind, placebo-controlled, two-period cross-over. Single oral dose of each medication for each of two attacks</p> <p>Medication administered when migraine headache pain of moderate or severe intensity</p> <p>Assessments at 0, 0.25, 0.5, 0.75, 1, 2, 3, 4, and 6 hours post-treatment</p> <p>If pain not controlled, participants asked to wait 2 hours before taking rescue medication</p>
Participants	<p>Aged > 18 years, meeting IHS criteria for migraine with and without aura. At least 12-month history of migraine, with one to six attacks per month within previous three months</p> <p>Excluded participants who vomited during the majority of their migraine attacks</p> <p>Excluded participants who regularly used NSAIDs or other drugs that could interact with trial medications</p> <p>N = 101 (73 treated two attacks and analysed for efficacy)</p> <p>M = 11, F = 90</p> <p>Mean age 44 years</p>
Interventions	Mouth-dispersible aspirin 900 mg, n = 73

MacGregor 2002 (Continued)

Placebo, n = 73

Outcomes	<p>Headache relief at all assessment time points</p> <p>Pain-free at all assessment time points</p> <p>PI: standard 4-point scale</p> <p>Functional disability: standard 4-point scale</p> <p>Presence/absence of associated symptoms</p> <p>Headache recurrence at 24 hours</p> <p>Use of rescue medication</p> <p>Participants' and investigators' global assessments</p> <p>Palatability and convenience of study medication</p>
Notes	Oxford Quality Score: R1, DB2, W1. Total score = 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"Placebo tablets formulated and manufactured to be indistinguishable from aspirin tablets, with respect to appearance, taste and dispersion in mouth"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Completer analysis (participants treating both attacks), but adequate reasons for exclusion given for others
Study size	Unclear risk	50 to 200 participants per treatment group

Tfelt-Hansen 1995

Methods	<p>Multicentre, randomised, double-blind, three parallel groups. Single oral dose per attack. Two attacks treated</p> <p>Medication taken when migraine headache pain of moderate or severe intensity</p> <p>Assessments at 0 and 2 hours</p> <p>If pain not controlled, participants asked to wait 2 hours before taking rescue medication</p>
Participants	<p>Aged 18-65 years, meeting IHS criteria for migraine with or without aura. At least 12-month history of migraine, with two to six attacks per month during three months prior to study</p> <p>N = 421 (385 experienced ≥ 1 attack and analysed for efficacy)</p> <p>M = 94, F = 327</p>

Tfelt-Hansen 1995 (Continued)

Mean age = 39 years

Interventions	Lysine acetylsalicylate 1620 mg (equivalent to 900 mg aspirin) plus metoclopramide 10 mg, n = 137 Sumatriptan 100 mg, n = 122 Placebo, n = 126
Outcomes	Headache relief at 2 hours PI: 4-point scale Pain-free at 2 hours 24-hour sustained relief Headache recurrence at 24 hours Relief of nausea and vomiting Use of rescue medication PGE: 4-point scale Adverse effects
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-dummy design
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data < 3%
Study size	Unclear risk	50 to 200 participants per treatment group

Thomson 1992

Methods	Multicentre, randomised, double-blind, parallel-group, double-dummy. Single oral dose per attack Participants treated up to three migraine attacks Assessments at 0 and 2 hours If pain not controlled, participants asked to wait 2 hours before taking rescue medication Participants instructed to leave minimum interval of 48 hours between consecutive study treatments to ensure adequate washout
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Thomson 1992 (Continued)

Participants	<p>Aged 18-65 years, meeting IHS criteria for migraine. At least 12-month history of migraine, with one to six attacks per month of moderate or severe intensity</p> <p>Excluded participants with need for continuing migraine prophylaxis</p> <p>N = 358 (355 analysed for at least one attack)</p> <p>M = 72, F = 283</p> <p>Mean age = 41 years</p>
Interventions	<p>Aspirin 900 mg plus metoclopramide 10 mg, n = 183</p> <p>Sumatriptan 100 mg, n = 172</p>
Outcomes	<p>Headache relief at 2 hours</p> <p>PI: 4-point scale</p> <p>Presence of nausea, vomiting, photophobia, phonophobia</p> <p>Functional disability</p> <p>Headache recurrence at 48 hours</p> <p>Use of rescue medication</p> <p>PGE: 4-point scale</p> <p>Adverse events</p>
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Double-dummy design
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Discrepancy between numbers in text and in Table 2. Numbers in text used: up to 15% missing data
Study size	Unclear risk	50 to 200 participants per treatment group

Titus 2001

Methods	<p>Multicentre, randomised, double-blind, parallel-group</p> <p>Medication taken up to three times at 2-hour intervals, if adequate relief not obtained, to treat a single migraine attack</p>
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Titus 2001 (Continued)

Rescue medication taken if no relief of symptoms after three doses of trial medication. Usual medication allowed if attack persisted 2 hours after second dose of trial medication

Assessments at 0 and 2 hours

Participants	<p>Aged 18-65 years, meeting IHS criteria for migraine</p> <p>Excluded participants with tension headache</p> <p>N = 227</p> <p>M = 34, F = 193</p> <p>Mean age 34 years</p>
Interventions	<p>Lysine acetylsalicylate 1620 mg (equivalent to 900 mg aspirin) plus metoclopramide 10 mg, n = 112</p> <p>Ergotamine 2 mg plus caffeine 200 mg, n = 115</p>
Outcomes	<p>No nausea or vomiting 2 hours after first intake</p> <p>Headache intensity (4-point categorical scale)</p> <p>Headache relief</p> <p>Complete resolution of headache</p> <p>Use of rescue medication</p> <p>Patients' global evaluation of treatment</p>
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Central randomisation list generated with SAS (PC version) 6.08"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"Maintained by providing an equivalent number of placebo sachets or capsules"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No useful efficacy data. Safety population accounted for
Study size	Unclear risk	50 to 200 participants per treatment group

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Chabriat 1993	Abstract (full data in Chabriat 1994)

Study	Reason for exclusion
Diener 2005	Mixed migraine and tension-type headaches
Limmroth 1999	Intravenous administration - self-administration not possible
Nebe 1995	Mixed migraine and tension-type headaches
Tfelt-Hansen 1980	Not randomised or double-blind
Tfelt-Hansen 1984	Included patients with mild headaches, headaches not IHS classified

DATA AND ANALYSES

Comparison 1. Aspirin 900 mg or 1000 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain free at 2 hours	6	2027	Risk Ratio (M-H, Fixed, 95% CI)	2.08 [1.70, 2.55]
2 Headache relief at 2 hours	6	2027	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [1.48, 1.83]
3 Headache relief at 1 hour	4	1288	Risk Ratio (M-H, Fixed, 95% CI)	2.13 [1.72, 2.63]
4 24-hour sustained headache relief	3	1142	Risk Ratio (M-H, Fixed, 95% CI)	1.63 [1.37, 1.95]
5 Pain free at 2 hours - effect of formulation	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Soluble	4	1230	Risk Ratio (M-H, Fixed, 95% CI)	1.92 [1.51, 2.44]
5.2 Tablet	2	797	Risk Ratio (M-H, Fixed, 95% CI)	2.47 [1.70, 3.58]
6 Headache relief at 2 hours - effect of formulation	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Soluble	4	1230	Risk Ratio (M-H, Fixed, 95% CI)	1.65 [1.43, 1.89]
6.2 Tablet	2	797	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [1.38, 1.95]
7 Relief of associated symptoms at 2 hours	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Nausea	4	878	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [1.10, 1.44]
7.2 Vomiting	3	139	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.94, 1.34]
7.3 Photophobia	5	1274	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [1.29, 1.69]
7.4 Phonophobia	5	1217	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [1.27, 1.64]

Analysis 1.1. Comparison 1 Aspirin 900 mg or 1000 mg versus placebo, Outcome 1 Pain free at 2 hours.

Analysis 1.2. Comparison 1 Aspirin 900 mg or 1000 mg versus placebo, Outcome 2 Headache relief at 2 hours.

Analysis 1.3. Comparison 1 Aspirin 900 mg or 1000 mg versus placebo, Outcome 3 Headache relief at 1 hour.

Analysis 1.4. Comparison 1 Aspirin 900 mg or 1000 mg versus placebo, Outcome 4 24-hour sustained headache relief.

Analysis 1.5. Comparison 1 Aspirin 900 mg or 1000 mg versus placebo, Outcome 5 Pain free at 2 hours - effect of formulation.

Analysis 1.6. Comparison 1 Aspirin 900 mg or 1000 mg versus placebo, Outcome 6 Headache relief at 2 hours - effect of formulation.

Analysis 1.7. Comparison 1 Aspirin 900 mg or 1000 mg versus placebo, Outcome 7 Relief of associated symptoms at 2 hours.

Comparison 2. Aspirin 900 mg plus metoclopramide 10 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain free at 2 hours	2	519	Risk Ratio (M-H, Fixed, 95% CI)	2.68 [1.59, 4.55]
2 Headache relief at 2 hours	3	765	Risk Ratio (M-H, Fixed, 95% CI)	2.15 [1.78, 2.60]
3 24-hour sustained headache relief	1	257	Risk Ratio (M-H, Fixed, 95% CI)	2.18 [1.39, 3.41]
4 Relief of associated symptoms at 2 hours	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Nausea	2	417	Risk Ratio (M-H, Fixed, 95% CI)	7.53 [4.20, 13.50]
4.2 Vomiting	2	59	Risk Ratio (M-H, Fixed, 95% CI)	16.14 [2.30, 113.05]

Analysis 2.1. Comparison 2 Aspirin 900 mg plus metoclopramide 10 mg versus placebo, Outcome 1 Pain free at 2 hours.

Analysis 2.2. Comparison 2 Aspirin 900 mg plus metoclopramide 10 mg versus placebo, Outcome 2 Headache relief at 2 hours.

Analysis 2.3. Comparison 2 Aspirin 900 mg plus metoclopramide 10 mg versus placebo, Outcome 3 24-hour sustained headache relief.

Analysis 2.4. Comparison 2 Aspirin 900 mg plus metoclopramide 10 mg versus placebo, Outcome 4 Relief of associated symptoms at 2 hours.

Comparison 3. Aspirin 900 mg or 1000 mg versus active comparator

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain free at 2 hours	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Sumatriptan 50 mg	2	726	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.65, 1.03]
2 Headache relief at 2 hours	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Sumatriptan 50 mg	2	726	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.84, 1.11]
3 Headache relief at 1 hour	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Sumatriptan 50 mg	2	726	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [1.26, 1.99]
4 Relief of associated symptoms at 2 hours	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Photophobia	2	575	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.81, 1.04]
4.2 Phonophobia	2	540	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.86, 1.11]

Analysis 3.1. Comparison 3 Aspirin 900 mg or 1000 mg versus active comparator, Outcome 1 Pain free at 2 hours.

Analysis 3.2. Comparison 3 Aspirin 900 mg or 1000 mg versus active comparator, Outcome 2 Headache relief at 2 hours.

Analysis 3.3. Comparison 3 Aspirin 900 mg or 1000 mg versus active comparator, Outcome 3 Headache relief at 1 hour.

Analysis 3.4. Comparison 3 Aspirin 900 mg or 1000 mg versus active comparator, Outcome 4 Relief of associated symptoms at 2 hours.

Comparison 4. Aspirin 900 mg plus metoclopramide 10 mg versus active comparator

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain free at 2 hours	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Sumatriptan 100 mg	2	528	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.45, 0.87]
2 Headache relief at 2 hours	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Sumatriptan 100 mg	2	523	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.79, 1.10]
3 Relief of associated symptoms at 2 hours	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Nausea	2	410	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.83, 1.46]
3.2 Vomiting	2	67	Risk Ratio (M-H, Fixed, 95% CI)	10.59 [1.43, 78.64]

Analysis 4.1. Comparison 4 Aspirin 900 mg plus metoclopramide 10 mg versus active comparator, Outcome 1 Pain free at 2 hours.

Analysis 4.2. Comparison 4 Aspirin 900 mg plus metoclopramide 10 mg versus active comparator, Outcome 2 Headache relief at 2 hours.

Analysis 4.3. Comparison 4 Aspirin 900 mg plus metoclopramide 10 mg versus active comparator, Outcome 3 Relief of associated symptoms at 2 hours. **Comparison 5. Aspirin ± metoclopramide versus placebo**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any adverse event within 24 hours	7	2458	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [1.02, 1.55]
1.1 Aspirin alone	5	1892	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [1.00, 1.68]
1.2 Aspirin + metoclopramide	2	566	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.82, 1.67]
2 Use of rescue medication	8	2922	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.63, 0.72]
2.1 Aspirin 100 mg alone	5	1881	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.61, 0.73]
2.2 Aspirin 900 mg + metoclopramide 10 mg	3	1041	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.62, 0.77]

Analysis 5.1. Comparison 5 Aspirin ± metoclopramide versus placebo, Outcome 1 Any adverse event within 24 hours.

Analysis 5.2. Comparison 5 Aspirin ± metoclopramide versus placebo, Outcome 2 Use of rescue medication.

Comparison 6. Aspirin ± metoclopramide versus active comparator

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any adverse event within 24 hours	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Aspirin versus sumatriptan 50 mg	2	730	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.61, 1.18]
1.2 Aspirin+met versus sumatriptan 100 mg	2	617	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.52, 0.84]
2 Use of rescue medication	4	1340	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [1.01, 1.28]
2.1 Aspirin versus sumatriptan 50 mg	2	726	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.92, 1.29]
2.2 Aspirin+met versus sumatriptan 100 mg	2	614	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [1.01, 1.39]

Analysis 6.1. Comparison 6 Aspirin ± metoclopramide versus active comparator, Outcome 1 Any adverse event within 24 hours.

Analysis 6.2. Comparison 6 Aspirin ± metoclopramide versus active comparator, Outcome 2 Use of rescue medication.

APPENDICES

Appendix 1. Definitions

All terms relating to primary efficacy outcomes are defined according to the effect of the treatment on headache pain, measured using a four-point pain intensity scale (ranging from 0 to 3 or none, mild, moderate, and severe).

- Baseline pain intensity - level of pain participant must be experiencing in order to receive study medication, either 1 (mild pain) or 2/3 (moderate or severe pain).
- Pain-free at 2 hours - number of participants with a pain intensity of 0 (none) at 2 hours after administration of study medication, expressed as a fraction of the treated participants with the appropriate baseline pain.
- Headache relief at 2 hours - number of participants with a reduction in pain intensity from 2/3 (moderate/severe) to 0/1 (none/mild) at 2 hours after administration of study medication, expressed as a fraction of the treated participants with grade 2/3 baseline pain.
- 24-hour sustained headache relief - number of participants with a reduction in pain intensity from 2/3 (moderate/severe) to 0/1 (none/mild) at 2 hours after administration of study medication which is then sustained between 2 and 24 hours without recurrence of headache or use of rescue medication, expressed as a fraction of the treated participants with grade 2/3 baseline pain.
- 24-hour sustained pain-free - number of participants with a pain intensity of 0 (none) at 2 hours after administration of study medication which is then sustained between 2 and 24 hours without recurrence of headache or use of rescue medication expressed as a fraction of the treated participants with the appropriate baseline pain.
- Use of rescue medication - number of participants requiring the use of additional medication to treat either recurrence of headache or an inadequate response to study medication, provided that the additional medication is not, or does not include, the study drug.

- Relief of associated symptoms - number of participants with an absence of a headache-associated symptom (nausea, vomiting, photophobia, or phonophobia) at 2 hours after administration of study medication, expressed as a fraction of the treated participants for whom the symptom was present at baseline.
- Relief of functional disability - reduction in the level of functional disability, measured using a four-point scale, from moderate or severe disability (grade 2/3) at baseline to mild or none (grade 1/0) at 2 hours after administration of study medication, expressed as a fraction of the treated participants with moderate or severe functional disability at baseline.

Appendix 2. Search strategy for MEDLINE (via Ovid)

1. Aspirin/
2. (aspirin OR acetylsalicylic acid OR ASA OR Migramax OR Migpriv OR Migrafin OR Migravess).mp
3. 1 OR 2
4. Headache/ OR exp Headache Disorders/
5. exp Migraine Disorders/
6. (headach* OR migrain* OR cephalgi* OR cephalalgi*).mp.
7. 4 OR 5 OR 6
8. randomized controlled trial.pt.
9. controlled clinical trial.pt.
- 10.randomized.ab.
- 11.placebo.ab.
- 12.drug therapy.fs.
- 13.randomly.ab.
- 14.trial.ab.
- 15.groups.ab.
- 16.OR/8-15
- 17.3 AND 7 AND 16

Appendix 3. Search strategy for EMBASE (via Ovid)

1. Acetylsalicylic acid/
2. (aspirin OR acetylsalicylic acid OR ASA OR Migramax OR Migpriv OR Migrafin OR Migravess).mp.
3. 1 OR 2
4. exp Headache and facial pain
5. exp migraine
6. (headach* OR migrain* OR cephalgi* OR cephalalgi*).mp.
7. 4 OR 5 OR 6
8. clinical trials.sh.
9. controlled clinical trials.sh.
- 10.randomized controlled trial.sh.
- 11.double-blind procedure.sh.
- 12.(clin* adj25 trial*).ab.
- 13.((doubl* or trebl* or tripl*) adj25 (blind* or mask*)).ab.
- 14.placebo*.ab.
- 15.random*.ab.
- 16.OR/8-15
- 17.3 AND 7 AND 16

Appendix 4. Search strategy for CENTRAL

1. MeSH descriptor Aspirin
2. (aspirin OR acetylsalicylic acid OR ASA OR Migramax OR Migpriv OR Migrafin OR Migravess):ti,ab,kw.
3. 1 OR 2
4. MeSH descriptor Headache/ OR MeSH descriptor Headache Disorders explode all trees
5. MeSH descriptor Migraine Disorders explode all trees
6. (headach* OR migrain* OR cephalgi* OR cephalalgi*):ti,ab,kw.
7. 4 OR 5 OR 6

8. Randomized controlled trial:pt
9. MESH descriptor Double-blind Method
- 10.random*:ti,ab,kw.
- 11.OR/8-10
- 12.3 AND 7 AND 11
- 13.Limit 12 to Clinical Trials (CENTRAL)

Appendix 5. Summary of outcomes: efficacy

Study ID	Treatment	HR 1 h	HR 2 h	PF 2 h	24 h SHR	24 h SPF	Use of rescue medication
Boureau 1994	(1) Aspirin 1000 mg, n = 198	No data	(1) 104/198	(1) 36/198	No data	No data	(1) 110/198
	(2) Paracetamol 400 mg + codeine 25 mg, n = 198		(2) 98/198	(2) 44/198			(2) 100/198
	(3) Placebo, n = 198		(3) 59/198	(3) 22/198			(3) 148/198
Chabriat 1994	(1) LAS 1650 mg (= 900 mg aspirin) + metoclopramide 10 mg, n = 126	No data	1st attack (1) 74/126	No usable data - denominator unclear	No usable data - total attacks	No data	Total attacks (1) 111/237
	(2) Placebo, n = 124		(2) 36/124				(2) 162/238
Diener 2004a	(1) Effervescent aspirin 1000 mg, n = 147	(1) 35/146	(1) 72/146	(1) 37/146	(1) 48/146	No data	(1) 62/146
	(2) Sumatriptan 50 mg, n = 135	(2) 31/135	(2) 66/135	(2) 33/135	(2) 47/135		(2) 53/135
	(3) Placebo, n = 153	(3) 23/152	(3) 50/152	(3) 22/152	(3) 33/152		(3) 98/152
Diener 2004b	(1) Effervescent aspirin 1000 mg, n = 222	(1) 76/221	(1) 116/221	(1) 60/221	(1) 93/221	No data	(1) 99/221
	(2) Ibuprofen 400 mg, n = 212	(2) 65/211	(2) 127/211	(2) 70/221	(2) 103/211		(2) 87/211
	(3) Sumatriptan 50 mg, n = 226	(3) 54/224	(3) 125/224	(3) 83/224	(3) 96/224		(3) 92/224
	(4) Placebo, n = 222	(4) 25/222	(4) 68/222	(4) 28/222	(4) 56/222		(4) 147/222
Geraud 2002	(1) Aspirin 900 mg + metoclopramide 10 mg, n = 340	No data	1st attack (1) 226/340	No usable data - average over 3 attacks	No usable data - denominator unclear	No data	Overall use: (1) 255/949
	(2) Zolmitriptan 2.5 mg, n = 326		(2) 197/326				(2) 229/909
Henry 1995	(1) Effervescent aspirin 900 mg + metoclopramide 10 mg, n = 152	No data	(1) 69/127* (2) 34/131*	(1) 18/127 (2) 7/131	No usable data - denominator unclear	No data	(1) 66/152 (2) 91/151
	(2) Placebo, n = 151						
Lange 2000	(1) Effervescent acetylsalicylic acid 1000 mg, n = 169	No data	(1) 93/169 (2) 64/174	(1) 49/169 (2) 29/174	No data	No data	(1) 65/169 (2) 100/174
	(2) Placebo, n = 174						

(Continued)

Le Jeunne 1998	(1) calcium carbasalate (= 900 mg aspirin) plus metoclopramide 10 mg, n = 134 (2) ergotamine tartrate 1 mg plus caffeine 100 mg, n = 132	No data	1st attack (1) 73/134 (2) 48/132	1st attack (1) 27/134 (2) 11/132	1st attack (1) 61/73 (2) 44/48	No data	1st attack (1) 49/134 (2) 61/131
Lipton 2005	(1) Aspirin 1000 mg, n = 205 (2) Placebo, n = 204	(1) 68/201 (2) 36/200	(1) 105/201 (2) 68/200	(1) 40/201 (2) 12/200	(1) 82/201 (2) 49/200	No data	(1) 68/201 (2) 104/200
MacGregor 2002	(1) Mouth-dispersible aspirin 900 mg, n = 73 (2) Placebo, n = 73	(1) 30/73 (2) 15/73	(1) 35/73 (2) 14/73	(1) 10/73 (2) 4/73	No usable data - recurrence less with aspirin	No usable data	No usable data - less with aspirin
Tfelt-Hansen 1995	(1) LAS 1620 mg (= 900 mg aspirin) + metoclopramide 10 mg, n = 137 (2) Sumatriptan 100 mg, n = 122 (3) Placebo, n = 126	No data	1st attack (1) 76/133 (2) 63/119 (3) 30/124	1st attack (1) 29/135 (2) 36/122 (3) 10/126	1st attack (1) 49/133 (2) 39/119 (3) 21/124	No data	1st attack (1) 74/137 (2) 77/122 (3) 102/126
Thomson 1992	(1) Aspirin 900 mg + metoclopramide 10 mg, n = 183 (2) Sumatriptan 100 mg, n = 175	No data	1st attack, in pts with mod/sev pain (1) 62/138 (2) 74/133	1st attack (1) 19/138 (2) 35/133	No usable data - data for 48 h	No data	1st attack (1) 102/183 (2) 59/175
Titus 2001	(1) LAS 1620 mg (= 900 mg aspirin) + metoclopramide 10 mg, n = 125 (2) Ergotamine 2 mg + caffeine 200 mg, n = 121	No data	No usable data	No usable data	No usable data	No usable data	No usable data

* 25 aspirin + metoclopramide and 20 placebo participants asleep

HR - headache relief; LAS - lysine acetylsalicylate; PF - pain-free; SHR - sustained headache relief; SPF - sustained pain-free

Appendix 6. Summary of outcomes: adverse events and withdrawals

Study ID	Treatment	Any AE	Specific AEs	Serious AEs	AE with- drawal	Other with- drawals/exclu- sions
Boureau 1994	(1) Aspirin 1000 mg, n = 198 (2) Paracetamol 400 mg + codeine 25 mg, n = 198 (3) Placebo, n = 198	(1) 29/198 (2) 36/198 (3) 27/198		None	None	12 pts excl from analyses because of serious protocol deviations
Chabriat 1994	(1) LAS 1650 mg (= 900 mg aspirin) + metoclopramide 10 mg, n = 126 (2) Placebo, n = 124	No usable data	"Minor and transient AE reported" (no numbers): - constipation - nausea - dizziness and/or vertigo	One patient reported epigastric pain one month after one dose of LAS-MCP and was found to have a gastric ulcer.	None	None
Diener 2004a	(1) Effervescent aspirin 1000 mg, n = 147 (2) Sumatriptan 50 mg, n = 135 (3) Placebo, n = 153	(1) 19/147 (2) 19/135 (3) 16/153	Gastrointestinal: (1) 5/147 (2) 7/135 (3) 7/153	None reported	None reported	2 pts excl from efficacy - did not return diary
Diener 2004b	(1) Effervescent aspirin 1000 mg, n = 222 (2) Ibuprofen 400 mg, n = 212 (3) Sumatriptan 50 mg, n = 226 (4) Placebo, n = 222	(1) 36/222 (2) 26/212 (3) 45/226 (4) 32/222	No data	(1) 1/222 (renal colic) (2) 1/212 (perforated duodenal ulcer) (3) 0/226 (4) 0/222	Possibly 2 serious AEs, but unconfirmed	1 treated pt excluded from analysis - did not return diary
Geraud 2002	(1) Aspirin 900 mg + metoclopramide 10 mg, n = 340 (2) Zolmitriptan 2.5 mg, n = 326	(1) 99/340 (2) 133/326	Most common: (1) Abdominal pain (5.0%), somnolence (5.0%), asthenia (4.9%) (2) vertigo (6.7%), somnolence (5.5%), paraesthesia (4.3%)	(1) 5/340 (2) 6/326	Over 3 attacks: (1) 5/340 (diarrhoea, palpitations + asthenia, anxiety + dry mouth, phlebitis) (2) 3/326	Details provided, but numbers are for entire study period and most due to failure to treat 3 attacks.

(Continued)

					(dizziness, somnolence, dizziness + vasodilatation)	
Henry 1995	(1) Effervescent aspirin 900 mg + metoclopramide 10 mg, n = 152 (2) Placebo, n = 151	(1) 31/152 (2) 28/151	Vomiting: (1) 8/152, (2) 15/151 Stomach ache: (1) 4/152, (2) 3/151 Somnolence: (1) 4/152, (2) 1/151	No data	None reported	None reported, but 45 pts were asleep and did not contribute to the 2 h efficacy evaluation
Lange 2000	(1) Effervescent acetylsalicylic acid 1000 mg, n = 169 (2) Placebo, n = 174	(1) 14/169 (2) 5/174	Most frequent body systems: (1) whole (5), digestive (3), nervous (3), respiratory (3) (2) whole (3)	None	None reported	None reported
Le Jeune 1998	(1) calcium carbasalate (= 900 mg aspirin) plus metoclopramide 10 mg, n = 134 (2) ergotamine tartrate 1 mg plus caffeine 100 mg, n = 132	Over 2 attacks: (1) 30/136 (2) 42/132	Any GI AE: (1) 9/136, (2) 28/132 Somnolence: (1) 6/136, (2) 5/132 Abdominal pain: (1) 5/136, (2) 12/132 Nausea: (1) 5/136, (2) 11/132	(1) 1/136 (pulmonary embolism) (2) 0/132	(1) 1/136 (pulmonary embolism) (2) 1/132 (back pain)	2 pts did not return diary cards
Lipton 2005	(1) Aspirin 1000 mg, n = 205 (2) Placebo, n = 204	(1) 18/205 (2) 10/204	Nausea: (1) 7/205 (2) 2/204 All other AE ≤1%	(1) 0/205 (2) 1/204 (perforated appendix)	Possibly one serious AE, but not confirmed	4 pts in each group treated non-migraine headaches, so excluded from efficacy analysis
MacGregor 2002	(1) Mouth-dispersible aspirin 900 mg, n = 73 (2) Placebo, n = 73	No usable data	Gastrointestinal: (1) 8/73 (dyspepsia, nausea, vomiting) (2) 4/73 (abdominal pain, nausea, vomiting)	(1) 1/73 (headache) (2) 1/73 (endometriosis)	(1) 4/73 (nausea, tinnitus, coughing, taste perversion) (2) 0/73	28 pts originally randomised were not included in analyses: insufficient attacks (6), unable to complete diary (7), withdrew consent (4), lost to follow-up (4) other (5)
Tfelt-Hansen 1995	(1) LAS 1620 mg (= 900 mg aspirin) + metoclopramide 10 mg, n = 137 (2) Placebo, n = 122	Over 3 attacks: (1) 25/137 (2) 37/122	Most common over 3 attacks: (1) somnolence, abdominal pain, nausea + vomiting	1 sumatriptan pt had acute AF requiring hospital admission	Over 3 attacks: (1) 1/138 (2) 4/125	32 pts originally randomised did not have any attacks and 4 took treatment but did

(Continued)

	(2) Sumatriptan 100 mg, n = 122 (3) Placebo, n = 126	(3) 18/126	(2) nausea + vomiting, fatigue, constriction of throat/chest pain, paraesthesia, somnolence, abdominal pain (3) nausea + vomiting, fatigue		(3) 2/126	not complete diaries
Thomson 1992	(1) Aspirin 900 mg + metoclopramide 10 mg, n = 183 (2) Sumatriptan 100 mg, n = 175	Over 3 attacks: (1) 53/183 (2) 74/175	Most common over 3 attacks: Nausea and/or vomiting: (1) 14/183, (2) 18/175 Malaise/fatigue: (1) 6/183, (2) 11/175 Dizziness/vertigo: (1) 4/183, (2) 9/175	No data	(1) 0/183 (2) 5/175 (headache + faintness + vomiting, scalp tingling + heaviness in chest + globus + prolonged aura, stomach pain, dyspnoea + heaviness in extremities, worsened headache + nausea)	3 pts excl from efficacy because did not return diary cards 87 pts excl from efficacy because had mild or no pain at baseline.
Titus 2001	(1) LAS 1620 mg (= 900 mg aspirin) + metoclopramide 10 mg, n = 125 (2) Ergotamine 2 mg + caffeine 200 mg, n = 121	Over multiple attacks and with possible multiple dosing: (1) 21/125 (2) 28/121	Most common over multiple attacks: (1) somnolence, diarrhoea, dyspepsia, nausea (2) abdominal pain, malaise, anxiety	None	(1) 1/125 (sinusitis) (2) 0/121	Lost to follow-up, non-cooperation, other: (1) 8/125 (2) 6/121
pts - participants						

Appendix 7. Other outcomes

Repeat dosing for a single attack

Studies frequently reported use of rescue medication (usually as a different medicine from that under test). Two reported use of a second (repeat) dose of the medicine under test for treating the same attack. This is a potentially useful strategy for nonprescription medicines. A second dose of study medication after 2 hours was used by just over half of each treatment group in [Geraud 2002](#), either because pain was not relieved or because it returned. Headache relief at 2 hours following the second dose occurred in a similar proportion to that following the first dose, with no difference between aspirin plus metoclopramide and zolmitriptan. In the other study permitting a second or third dose of study medication to treat a single attack, just under half of each treatment group (aspirin plus metoclopramide and ergotamine plus caffeine) used a second dose, but no data were reported for our primary efficacy outcomes ([Titus 2001](#)).

Multiple attacks

Response to therapy after a single migraine attack is useful knowledge, but migraineurs will suffer many attacks, and knowledge is needed about consistency of response. Few studies gave useful information on response in multiple attacks. However, five studies provided data for headache relief at 2 hours separately for two ([Chabriot 1994](#); [Le Jeunne 1998](#); [Tfelt-Hansen 1995](#)) or three ([Geraud 2002](#); [Thomson 1992](#)) consecutive attacks treated with the same medication. Response rates either increased compared with the first attack by up to 9%, or

decreased by up to 11%. There was no consistent pattern of change either within a treatment group (Figure 6) or between treatments (aspirin plus metoclopramide and control). All changes are within those that might be expected by the play of chance.

Figure 6. Response rates for aspirin 900 mg plus metoclopramide 10 mg in consecutive attacks, reported in five studies (from left: Tfelt-Hansen 1995; Chabriat 1994; Thomson 1992; Le Jeune 1998; Geraud 2002)

Use of rescue medication

All studies asked participants whose symptoms were not adequately controlled to wait for 2 hours before taking any additional medication in order to give the test medication enough time to have an effect. Use of rescue or 'escape' medication (usually a different analgesic) after that time and up to 24 hours after dosing was reported in all studies and is a measure of treatment failure (lack of efficacy). In the study allowing multiple dosing for a single attack (Titus 2001), use of a second dose of study medication was interpreted as use of rescue medication for this analysis (Figure 7).

Figure 7. Forest plot of comparison: 5 Aspirin ± metoclopramide versus placebo, outcome: 5.2 Use of rescue medication.

Summary of results: Use of rescue medication

Placebo comparators	Studies	Attacks treated	Treatment (%)	Comparator (%)	Relative risk (95% CI)	NNTp (95% CI)
Aspirin (± metoclopramide) versus placebo (Analysis 5.2)	8	2922	44	65	0.68 (0.63 to 0.73)	4.8 (4.1 to 5.7)
Aspirin 1000 mg versus placebo	5	1881	42	63	0.67 (0.61 to 0.73)	4.8 (3.9 to 6.0)
Aspirin 900 mg plus metoclopramide 10 mg versus placebo	3	1041	48	69	0.69 (0.62 to 0.77)	4.7 (3.7 to 6.5)
Active comparators	Studies	Attacks treated	Treatment (%)	Comparator (%)	Relative risk (95% CI)	NNH (95% CI)
Aspirin (± metoclopramide) versus sumatriptan 50 mg or 100 mg (Analysis 6.2)	4	1340	49	43	1.1 (1.01 to 1.3)	17 (8.8 to 140)
Aspirin 1000 mg versus sumatriptan 50 mg	2	726	44	40	1.1 (0.92 to 1.3)	Not calculated
Aspirin 900 mg plus metoclopramide 10 mg versus sumatriptan 100 mg	2	614	55	46	1.2 (1.01 to 1.4)	11 (6.0 to 120)

Relief of headache-associated symptoms

In general, relief of headache-associated symptoms (defined as a symptom reduction from moderate or severe to mild or none) was inconsistently reported. Of the eight studies that reported dichotomous data for symptom relief and comparing aspirin with placebo (Boureau 1994; Chabriat 1994; Diener 2004a; Diener 2004b; Lange 2000; Lipton 2005; MacGregor 2002; Tfelt-Hansen 1995), only one study provided data for all four symptoms of interest (Lange 2000). The 900 mg aspirin dose used in one study (MacGregor 2002) was assumed to have the same efficacy as 1000 mg aspirin. Although two studies with an aspirin plus metoclopramide treatment arm provided data for relief of nausea and vomiting (Chabriat 1994; Tfelt-Hansen 1995), there were no data available for the effects of this combination treatment on relief of photophobia and phonophobia.

Two studies (Tfelt-Hansen 1995; Thomson 1992) provided data on relief of nausea and of vomiting for aspirin plus metoclopramide versus sumatriptan 100 mg (Analysis 4.3), and two (Diener 2004a; Diener 2004b) provided data on relief of photophobia and of phonophobia versus sumatriptan 50 mg (Analysis 3.4). Five studies compared aspirin to other active migraine treatments for relief of headache-associated symptoms (Boureau 1994; Diener 2004b; Geraud 2002; Le Jeunne 1998; Titus 2001), but there were insufficient data for analysis. In this update, a small correction has been made to the placebo denominator for photophobia in Lange 2000; the result is not significantly changed.

Aspirin alone significantly relieved all symptoms except vomiting compared with placebo (Analysis 1.7), while aspirin plus metoclopramide significantly relieved both nausea and vomiting compared to placebo (Analysis 2.4). Subgroup analysis showed a statistically significant difference in favour of aspirin plus metoclopramide over aspirin alone for relief of nausea at two hours ($z = 5.595$, $P < 0.00006$), and relief of vomiting at two hours ($z = 3.131$, $P = 0.002$). Aspirin plus metoclopramide relieved more vomiting, but not nausea, compared to sumatriptan 100 mg (Analysis 4.3), while aspirin alone was not significantly different from sumatriptan 50 mg for relief of photophobia or phonophobia (Analysis 3.4).

Summary of results: Relief of associated symptoms 2 hours after taking study medication

Intervention	Studies	Attacks with symptom present	Treatment (%)	Placebo (%)	Relative risk (95% CI)	NNT
Nausea						
Aspirin 1000 mg versus placebo	4	878	56	44	1.3 (1.1 to 1.4)	9.0 (5.6 to 22)
Aspirin 900 mg plus metoclopramide 10 mg versus placebo	2	417	45	6	7.5 (4.2 to 14)	2.6 (2.1 to 3.1)
Aspirin 900 mg plus metoclopramide 10 mg versus sumatriptan 100 mg	2	410	35	31	1.1 (0.83 to 1.5)	Not calculated
Vomiting						
Aspirin 1000 mg versus placebo	3	139	73	66	1.1 (0.94 to 1.3)	Not calculated
Aspirin 900 mg plus metoclopramide 10 mg versus placebo	2	59	46	0	17 (2.3 to 120)	2.1 (1.5 to 3.7) [12 events]
Aspirin 900 mg plus metoclopramide 10 mg versus sumatriptan 100 mg	2	67	33	0	11 (1.4 to 78)	3.3 (2.1 to 7.4) [11 events]
Photophobia						
Aspirin 1000 mg versus placebo	5	1274	47	31	1.5 (1.3 to 1.7)	6.6 (4.9 to 10)

(Continued)

Aspirin 1000 mg versus sumatriptan 50 mg	2	575	60	66	0.91 (0.80 to 1.03)	Not calculated
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Phonophobia

Aspirin 1000 mg	5	1217	49	34	1.4 (1.3 to 1.7)	6.6 (4.9 to 10)
Aspirin 1000 mg versus sumatriptan 50 mg	2	540	63	65	0.98 (0.86 to 1.1)	Not calculated

Functional disability

Only one study with 73 participants reported data on functional disability (MacGregor 2002). More individuals with moderate or severe disability reported improvement following treatment with aspirin (22/53) than with placebo (3/61).

WHAT'S NEW

Date	Event	Description
29 May 2019	Amended	Contact details updated.
11 October 2017	Review declared as stable	No new studies likely to change the conclusions are expected.

HISTORY

Protocol first published: Issue 4, 2009

Review first published: Issue 4, 2010

Date	Event	Description
6 September 2017	Review declared as stable	See Published notes .
22 June 2015	Amended	An error in data extraction (Deiner 2004a, HR1) was brought to the attention of the authors. This has been corrected with only a small change in the results and no change in the conclusions
7 May 2013	Review declared as stable	This review will be assessed for further updating in 2018.
5 February 2013	New citation required but conclusions have not changed	No new studies identified.
5 February 2013	New search has been performed	New searches carried out, Risk of bias tables expanded and updated, Summary of findings table added.
24 September 2010	Amended	Contact details updated.

CONTRIBUTIONS OF AUTHORS

All authors were involved with planning and writing the protocol. For the original review, VK and SD carried out the searches, identified studies for inclusion, extracted data and performed analyses. RAM helped with analyses, HJM acted as arbitrator, and all review authors were involved with writing.

For the update, SD and KV searched for new studies and updated the Risk of bias table and SD and RAM created the Summary of findings table. SD updated the RevMan file.

DECLARATIONS OF INTEREST

VK has no interests to declare. RAM has consulted for various pharmaceutical companies and received lecture fees from pharmaceutical companies related to analgesics and other healthcare interventions. RAM and SD have received research support from charities, government and industry sources at various times. Support for the original review was from Pain Research Funds, the NHS Cochrane Collaboration Programme Grant Scheme, and the NIHR Biomedical Research Centre Programme. None had any input into the review at any stage.

SOURCES OF SUPPORT

Internal sources

- Oxford Pain Relief Trust, UK.
General institutional support

External sources

- International Headache Society, UK.
Support for the editorial process

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the original review we considered data on three outcomes not specified in the protocol.

1. Use of rescue medication was reported by the majority of studies, and provides a measure of efficacy from the point of view of the patient. In taking rescue medication the patient is saying that the efficacy of the medication is not adequate and that they need alternative analgesia. They are effectively withdrawing due to lack of efficacy, where efficacy is defined by their preparedness to carry on without additional analgesia, rather than a predefined outcome such as headache relief at two hours. We believe this is useful additional information relevant to clinical practice.
2. Using a second (repeat) dose of the medication to treat the same attack is a potentially useful strategy for nonprescription medicines. Although few of the studies in this review reported this outcome, we included it because of its relevance to clinical practice.
3. Headache relief over multiple (two or three) attacks was reported in five studies. We chose to analyse this because it provides useful information about whether initial response to medication is maintained in subsequent attacks.

After discussion with headache specialists and editorial staff, and in line with Cochrane recommendations, we decided to limit our outcomes for acute migraine headache reviews in order to focus attention on the most important outcomes and to make them more readable for both clinicians and patients. For the majority of interventions we will now include 2-hour pain-free and headache relief (PF2 and HR2) as primary outcomes, and 24-hour sustained pain-free and headache relief (SPF24 and SHR24) and adverse events as secondary outcomes. In this update we have moved results for use of rescue medication and relief of headache-associated symptoms and functional disability to [Appendix 7](#).

In the update we have expanded the Risk of bias table; this review uses the new criteria for analysis. We have also included an assessment of publication bias, which was not included in the protocol or original review. This assessment is now being added routinely to all our reviews as a measure of reliability and robustness of the results.

NOTES

A restricted search in September 2017 did not identify any potentially relevant studies. Therefore, this review has now been stabilised following discussion with the authors and editors. If appropriate, we will update the review if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Inflammatory Agents, Non-Steroidal [*therapeutic use]; Antiemetics [*therapeutic use]; Aspirin [*therapeutic use]; Drug Therapy, Combination [methods]; Metoclopramide [therapeutic use]; Migraine Disorders [complications] [*drug therapy]; Nausea [drug therapy] [etiology]; Photophobia [drug therapy] [etiology]; Randomized Controlled Trials as Topic; Sumatriptan [therapeutic use]; Vomiting [drug therapy] [etiology]

MeSH check words

Adult; Humans