Cochrane Library

Cochrane Database of Systematic Reviews

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

Rabbie R, Derry S, Moore RA

Rabbie R, Derry S, Moore RA.
Ibuprofen with or without an antiemetic for acute migraine headaches in adults.
Cochrane Database of Systematic Reviews 2013, Issue 4. Art. No.: CD008039.
DOI: 10.1002/14651858.CD008039.pub3.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

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

Roy Rabbie[1], Sheena Derry[2], R Andrew Moore[3]

[1]Department of Respiratory Medicine, Epsom and St Helier University Hospitals NHS Trust, London, UK. [2]Oxford, UK. [3]Plymouth, UK

Contact address: Sheena Derry, Oxford, Oxfordshire, UK. sheena.derry@retired.ox.ac.uk.

Editorial group: Cochrane Pain, Palliative and Supportive Care Group.
Publication status and date: Stable (no update expected for reasons given in 'What's new'), published in Issue 5, 2019.

Citation: Rabbie R, Derry S, Moore RA. Ibuprofen with or without an antiemetic for acute migraine headaches in adults. *Cochrane Database of Systematic Reviews* 2013, Issue 4. Art. No.: CD008039. DOI: 10.1002/14651858.CD008039.pub3.

ABSTRACT

Background

This is an updated version of the original review published in Issue 10, 2010 (Rabbie 2010). Migraine is a common, disabling condition and a burden for the individual, health services and society. Many sufferers do not seek professional help, relying instead on over-the-counter analgesics. Co-therapy with an antiemetic should help to reduce symptoms commonly associated with migraine headaches.

Objectives

To determine efficacy and tolerability of ibuprofen, 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 22 April 2010 for the original review and to 14 February 2013 for the update.

Selection criteria

We included randomised, double-blind, placebo- or active-controlled studies using self-administered ibuprofen 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 number needed to treat (NNT) or harm (NNH) compared to placebo or other active treatment.

Main results

No new studies were found for this update. Nine included studies (4373 participants, 5223 attacks) compared ibuprofen with placebo or other active comparators; none combined ibuprofen with a self-administered antiemetic. All studies treated attacks with single doses of medication. For ibuprofen 400 mg versus placebo, NNTs for 2-hour pain-free (26% versus 12% with placebo), 2-hour headache relief (57% versus 25%) and 24-hour sustained headache relief (45% versus 19%) were 7.2, 3.2 and 4.0, respectively. For ibuprofen 200 mg versus placebo, NNTs for 2-hour pain-free (20% versus 10%) and 2-hour headache relief (52% versus 37%) were 9.7 and 6.3, respectively. The higher dose was significantly better than the lower dose for 2-hour headache relief. Soluble formulations of ibuprofen 400 mg were better than standard tablets for 1-hour, but not 2-hour headache relief.

Similar numbers of participants experienced adverse events, which were mostly mild and transient, with ibuprofen and placebo.

Ibuprofen 400 mg did not differ from rofecoxib 25 mg for 2-hour headache relief or 24-hour headache relief.

Authors' conclusions

We found no new studies since the last version of this review. Ibuprofen is an effective treatment for acute migraine headaches, providing pain relief in about half of sufferers, but complete relief from pain and associated symptoms for only a minority. NNTs for all efficacy outcomes were better with 400 mg than 200 mg in comparisons with placebo, and soluble formulations provided more rapid relief. Adverse events were mostly mild and transient, occurring at the same rate as with placebo.

PLAIN LANGUAGE SUMMARY

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

This is an updated version of the original Cochrane review published in Issue 10, 2010 (Rabbie 2010); no new studies were found. A single oral dose of ibuprofen 200 mg or 400 mg is effective in relieving pain in migraine headaches. Pain will be reduced from moderate or severe to no pain by two hours in just over 1 in 4 people (26%) taking ibuprofen 400 mg, compared with about 1 in 10 (12%) taking placebo. It will be reduced from moderate or severe to no worse than mild pain by two hours in roughly 1 in 2 people (57%) taking ibuprofen compared with approximately 1 in 4 (25%) taking placebo. Of those who experience effective headache relief at two hours, more have that relief sustained over 24 hours with ibuprofen than with placebo. A 200-mg dose is slightly less effective, while soluble formulations give more rapid responses. A single 400-mg dose of ibuprofen has efficacy similar to that shown for a single dose of 1000 mg aspirin in a separate Cochrane review (Kirthi 2013).

Adverse events are mostly mild and transient, occurring in the same proportion of participants treated with ibuprofen and placebo. Very few individuals had serious adverse events or needed to withdraw from these studies because of adverse events.

There is no information for ibuprofen combined with a self-administered antiemetic, and little information comparing ibuprofen with other medications. There were no significant differences between ibuprofen 400 mg and rofecoxib 25 mg (now withdrawn) for 2-hour headache relief, 24-hour sustained headache relief, or use of rescue medication.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Ibuprofen 400 mg compared with placebo for migraine headache

Patient or population: adults with migraine headache - moderate or severe pain
Settings: community
Intervention: ibuprofen 400 mg
Comparison: placebo

Outcomes	Probable outcome with intervention	Probable outcome with comparator	NNT or NNTH and/or relative effect (95% CI)	No of studies, attacks, events	Quality of the evidence (GRADE)	Comments
Pain free response at 2 h	260 in 1000	120 in 1000	NNT 7.2 (5.9 to 9.2)	6 studies, 2575 attacks, 529 events	Moderate[1]	
Headache relief at 2 h	250 in 1000	570 in 1000	NNT 3.2 (2.8 to 3.7)	7 studies, 1815 attacks, 752 events	Moderate[1]	
Sustained pain-free at 24 h	no data					
Sustained headache relief at 24 h	190 in 1000	450 in 1000	NNT 4.0 (3.2 to 5.2)	4 studies, 879 attacks, 288 events	Moderate[1]	
At least one AE	180 in 1000	150 in 1000	NNH 26 (15 to 100)	8 studies, 2722 attacks, 441 events	Moderate[1]	
Serious AE	insufficient data					

CI: Confidence interval; **NNT**: number needed to treat; **NNH**: number needed to harm

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

Description of the condition

Migraine is a common, disabling headache disorder, ranked seventh highest among specific causes of disability globally (Steiner 2013), with considerable social and economic impact (Hazard 2009). Recent surveys found a one-year prevalence of 15% globally (Vos 2012) and for adults in European countries (Stovner 2010), 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 and/or photophobia and phonophobia. 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 Europena Union (EU) countries (representing 55% of the adult population) has estimated an annual direct and indirect cost of migraine per person of EURO1222, and a total annual cost for the EU of EURO111 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 they 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

Ibuprofen is an effective and well-tolerated NSAID that has been available as an OTC medication in the United Kingdom (UK) and US for 25 years. Ibuprofen is a propionic acid derivative with analgesic, anti-inflammatory and antipyretic properties. It has been widely used in treating arthritis, dental pain, menstrual cramps and a variety of other acute pain conditions; the usual recommended adult dose for acute pain is 400 mg up to three times daily. OTC medications are less expensive, more accessible and have favourable safety profiles relative to many prescription treatments. Ibuprofen is an attractive candidate for OTC migraine headache treatment.

In order to establish whether ibuprofen 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

NSAIDs act by inhibiting the activity of cyclooxygenase (COX), now recognised to consist of two isoforms (COX-1 and COX-2), which catalyses the production of prostaglandins responsible for pain and inflammation. Ibuprofen inhibits both COX isoforms. Suppression of prostaglandin synthesis is believed to underlie the analgesic effects of ibuprofen.

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 im-

prove 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. This has been investigated for metoclopramide and aspirin (Ross-Lee 1983; Volans 1975). It has been claimed that treatment with intravenous metoclopramide alone can reduce pain in severe migraine attacks (Friedman 2005; Salazar-Tortolero 2008), but this claim requires further investigation, since metoclopramide has not been shown to be an analgesic in classical pain studies. The present review will seek to determine whether treatment of acute migraine attacks with ibuprofen plus an antiemetic is in any way superior to treatment with ibuprofen alone. In a recent review of aspirin with or without an antiemetic for acute migraine (Kirthi 2013), aspirin plus metoclopramide was significantly better than aspirin alone for headache relief and relief of nausea at two hours, but not pain-free at two hours or 24 hours.

Why it is important to do this review

Population surveys show that ibuprofen is frequently used to treat migraine headaches, but we could find no comprehensive systematic review of the efficacy of this intervention in adults. Ibuprofen has proven efficacy in a variety of acute pain situations, is widely available and inexpensive, and it is important to know where it 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.

This review is one of a series examining the efficacy of OTC treatments for migraine, including aspirin (Kirthi 2013), paracetamol (acetaminophen; Derry 2013a), and diclofenac (Derry 2013), 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 ibuprofen, 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- or active-controlled studies using ibuprofen 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 below. We accepted studies reporting treatment of consecutive headache episodes if outcomes for the first, or each, episode were reported separately; first-attack data were used preferentially. We accepted cross-over studies if there was adequate washout (at least 24 hours) between treatments.

Types of participants

Studies enrolled adults (at least 18 years of age) with migraine. We used the definition of migraine specified by the International Headache Society (IHS 1988; IHS 2004), although we accepted diagnostic criteria equivalent to IHS 1988, where a specific reference was not provided. 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 ibuprofen 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 ibuprofen alone, or ibuprofen plus an antiemetic. The antiemetic had to be taken either combined with ibuprofen in a single formulation, or separately not more than 30 minutes before ibuprofen, and had to be self-administered.

A placebo comparator is essential to demonstrate that ibuprofen 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 headaches.

Types of outcome measures

In selecting the main outcome measures for this review, we considered scientific rigour, availability of data and patient preferences. 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 outcomes at one hour would also be collected if reported and relevant, for example if a fast-acting formulation of the intervention was tested.

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.

Other outcomes

Data for a number of other outcomes were also collected, including:

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

Pain intensity or pain relief had to be measured by the patient (not the investigator or care giver). Pain measures accepted for the main efficacy 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. Definitions of important terms, including all measured outcomes, are provided in Appendix 1.

Search methods for identification of studies

Electronic searches

The following electronic databases were searched for the original review:

- The Cochrane Central Register of Controlled Trials (CENTRAL), last search 22 April 2010.
- MEDLINE (via Ovid) last search 22 April 2010.
- EMBASE (via Ovid) last search 22 April 2010.
- Oxford Pain Relief Database (Jadad 1996a).

For the update we searched:

- The Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 1, 2013);
- MEDLINE (via Ovid) from 1 January 2010 to 14 February 2013;
- EMBASE (via Ovid) from 1 January 2010 to 14 February 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 http://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 the titles and abstracts of all studies identified by 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.

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.

The following terms were used to describe adverse outcomes in terms of harm or prevention of harm:

- When significantly fewer adverse outcomes occurred with ibuprofen 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 occurred with ibuprofen 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 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 ≥ 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 ≥ 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 ibuprofen 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 included the number one.

We used the z test to determine significant differences between NNT, NNTp and 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 subgroup analysis were dose, monotherapy or 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

Results of the search

New searches in February 2013 did not identify any additional studies. Thirteen studies were identified as potentially suitable for the original review. We were aware that two unpublished studies may have been performed by a pharmaceutical company some years ago, but were unable to obtain any useful information and had no direct knowledge that they actually existed; trial reports could not be retrieved at the time of writing the original review, and no further information was available for inclusion in this update.

Included studies

Nine studies fulfilled the entry criteria (Codispoti 2001; Diener 2004; Ellis 1993; Goldstein 2006; Kellstein 2001; Misra 2004; Misra 2007; Sandrini 1998; Saper 2006). Included participants all had a diagnosis of migraine headaches according to IHS criteria (IHS 1988), except in one study which predated these but used criteria compatible with them (Ellis 1993). The mean age of participants was 30 to 40 years in individual studies. Misra 2004 and Misra 2007 included participants as young as 16 years, and just under 5% of participants in Kellstein 2001 were aged 16 to 19 years. We accepted these studies because the proportion of individuals under 18 years old was low, they satisfied IHS diagnostic criteria and could be expected to need adult dosing regimens.

In most studies participants had a history of migraine symptoms for at least 12 months before entering the study, but in one (Saper 2006) it was at least 6 months, and in two studies (Ellis 1993; Misra 2007) this information was not reported. One study (Codispoti 2001) enrolled participants on stable prophylactic therapy provided it continue unchanged. The remaining studies did not mention use of prophylactic therapy; it is likely that it was not permitted.

Four studies (Codispoti 2001; Kellstein 2001; Misra 2004; Misra 2007) excluded participants who experienced headaches that were usually severely disabling or incapacitating, and/or accompanied at least 20% of the time by vomiting, while Goldstein 2006 specifically did not exclude such participants. The remaining studies did not mention exclusions due to the usual degree of incapacity or vomiting associated with attacks.

Seven studies used a parallel-group design: five of these (Codispoti 2001; Ellis 1993; Goldstein 2006; Kellstein 2001; Saper 2006) treated a single attack with a single dose of study medication, while two (Misra 2004; Misra 2007) treated two or more attacks with single doses of the same study medication. It is not clear how the data for multiple attacks were combined in these studies; we have included them on the assumption that an individual's response was consistent across attacks, given that a sensitivity analysis was to be carried out excluding these studies on the grounds of potentially unreliable blinding (see Risk of bias in included studies, below).

Two studies used a cross-over design: in Diener 2004 participants treated three separate attacks with single doses of three different study medications, while in Sandrini 1998 participants treated two consecutive attacks with single doses of two different study medications. Neither study reported data for the first attack only.

Three studies had only a placebo comparator (Codispoti 2001; Kellstein 2001; Sandrini 1998), and six had both placebo and active comparators. The active comparators were aspirin and sumatriptan (Diener 2004), rizatriptan (Misra 2007; Saper 2006), rofecoxib (Misra 2004), intravenous metoclopramide (Ellis 1993) and a combination of paracetamol, aspirin and caffeine (Goldstein 2006). Of the six active comparators, however, only rofecoxib 25 mg provided sufficient data for analysis. No study compared ibuprofen alone with ibuprofen plus an antiemetic using a formulation that could be self-administered: the study that used intravenous metoclopramide (Ellis 1993) did not report any dichotomous efficacy outcomes. All studies treated an attack with a single dose of study medication when pain was of at least moderate severity. No studies investigated treating attacks when pain was mild, and none compared different dosing strategies or treatment

regimens.

In total, 414 participants were treated with ibuprofen 200 mg, 1615 with ibuprofen 400 mg, 208 with ibuprofen 600 mg, 1127 with placebo, and 1145 with other active comparators. In most studies ibuprofen was administered as a standard oral tablet, but Kellstein 2001 used an oral liquigel formulation (solubilised ibuprofen potassium), and Sandrini 1998 used oral ibuprofen arginine. These two formulations are combined as "soluble" formulations for analysis in this review. The more soluble formulations are thought to enhance drug absorption and produce higher or earlier peak plasma concentrations.

One study (Sandrini 1998) measured headache relief using a standard 5 point scale, and reported the numbers of participants with "considerable/complete relief" (the top two points). We used this number as equivalent to pain reduced to mild or none on a standard 4 point scale in the analysis of headache relief at one and two hours.

See Characteristics of included studies for details of individual included studies. Ellis 1993 did not report any usable dichotomous data except for use of rescue medication.

Excluded studies

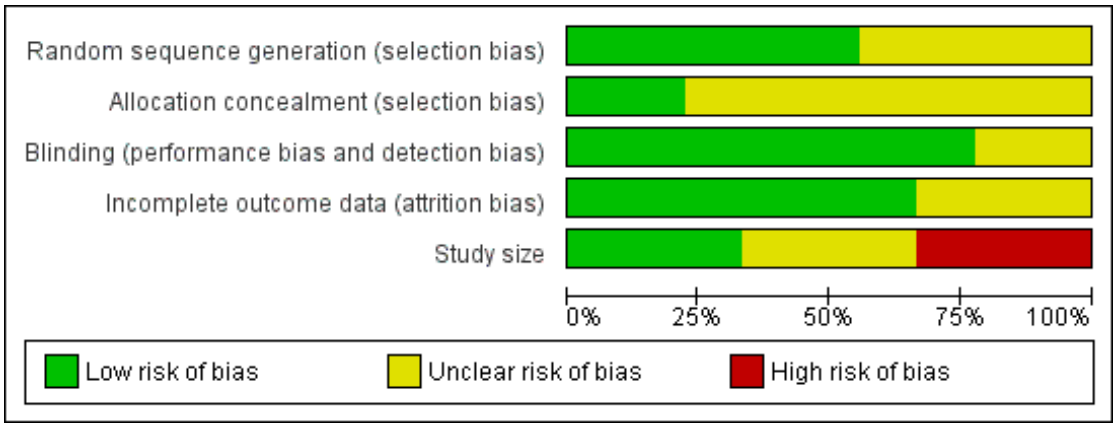
Five studies (Havanka 1989; Kalita 2009; Kloster 1992, Nebe 1995; Pearce 1983) were excluded after reading the full report. Reasons for exclusion are provided in the Characteristics of excluded studies table.

Risk of bias in included studies

All studies were randomised and double-blind, and all except one (Ellis 1993) reported on withdrawals and dropouts. One study (Codispoti 2001) scored 5 of 5, six scored 4 of 5 (Diener 2004; Goldstein 2006; Kellstein 2001; Misra 2004; Misra 2007; Sandrini 1998; Saper 2006), and one scored 3 of 5 (Ellis 1993) on the Oxford Quality Scale. Points were lost mainly because of failure to adequately describe the methods of randomisation and blinding. Details are provided in the Characteristics of included studies table. In two of the studies (Misra 2004; Misra 2007) there is some doubt about the effectiveness of the double-blinding since the tablets had identical packets, but were not identical in appearance. We have included them as double-blind, and carried out a sensitivity analysis to see whether their inclusion influences the results. Misra 2004 also excluded from analysis more than 10% of treated participants because they were lost to follow-up.

A risk of bias table was completed for randomisation, allocation concealment, blinding, incomplete outcome data, and study size. Only two studies (Codispoti 2001; Saper 2006) adequately described the method of allocation concealment, while three studies (Ellis 1993; Misra 2004; Sandrini 1998) were considered at high risk of bias due to small treatment group size (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**

Details of outcomes in individual studies are provided in Appendix 5 (efficacy) and Appendix 6 (adverse events and withdrawals).

Pain-free at two hours

Ibuprofen 200 mg versus placebo

Two studies provided data for pain-free response at two hours (777 participants). One study used a standard oral formulation (Codispoti 2001) and the other a liquigel formulation (Kellstein 2001).

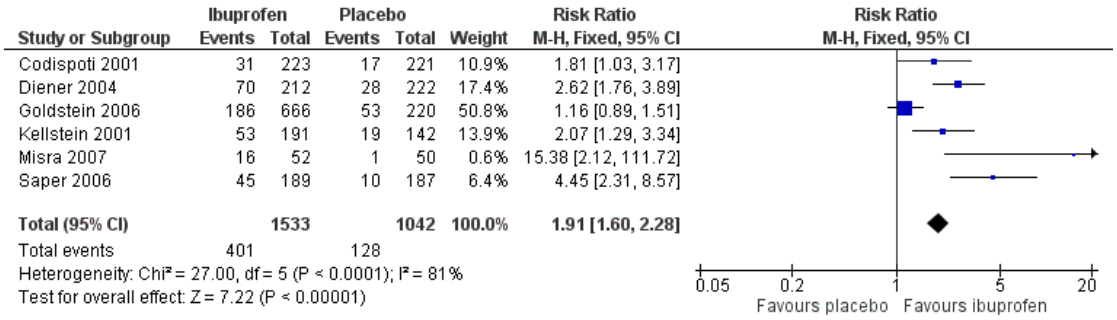
- The proportion of participants pain-free at two hours with ibuprofen 200 mg was 20% (84/414; range 16% to 25%).
- The proportion of participants pain-free at two hours with placebo was 10% (36/363; range 8% to 13%).
- The relative benefit of treatment compared to placebo was 2.0 (95% CI 1.4 to 2.8); the NNT was 9.7 (6.5 to 18) (Analysis 1.1).

Ibuprofen 400 mg versus placebo

Six studies provided data for pain-free response at two hours (2575 participants). Five studies used a standard oral formulation (Codispoti 2001; Diener 2004; Goldstein 2006; Misra 2007; Saper 2006) and one study used a liquigel formulation (Kellstein 2001).

- The proportion of attacks pain-free at two hours with ibuprofen 400 mg was 26% (401/1553; range 14% to 33%).
- The proportion of attacks pain-free at two hours with placebo was 12% (128/1042; range 2% to 24%).
- The relative benefit of treatment compared to placebo was 1.9 (1.6 to 2.3); the NNT was 7.2 (5.9 to 9.2). (Analysis 2.1; Figure 2).

Figure 2. Forest plot of comparison: 2 Ibuprofen 400 mg versus placebo, outcome: 2.1 Pain-free at 2 hours.



Subgroup analysis for formulation

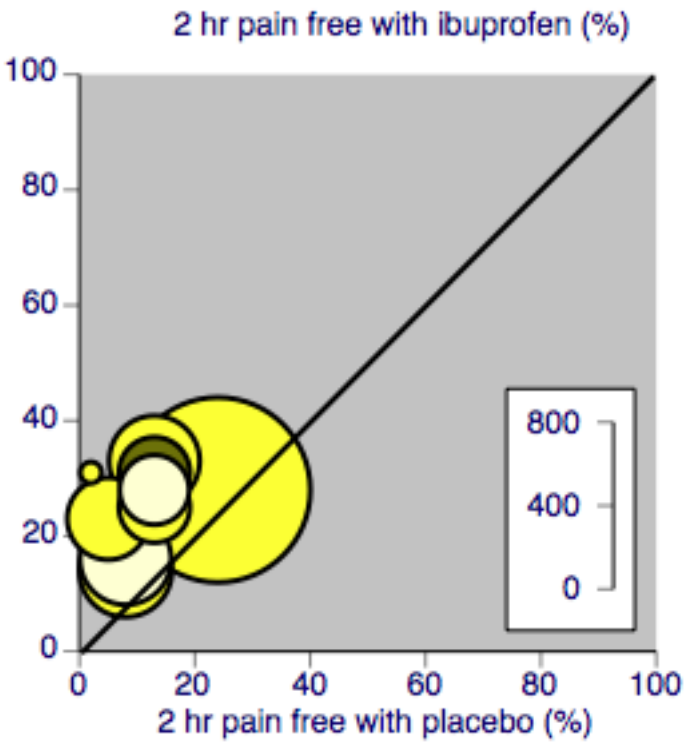
For the five studies using standard formulations (2242 attacks), the NNT was 7.2 (5.9 to 9.4).

Ibuprofen 600 mg versus placebo

Only one study (Kellstein 2001) provided data for pain-free response at two hours (340 participants): 29% of participants had this outcome with ibuprofen 600 mg compared with 13% with placebo.

A L'Abbé plot for this outcome shows consistency of response with different doses (Figure 3).

Figure 3. L'Abbé plot showing 2-hour pain-free response for ibuprofen versus placebo. Size of circle is proportional to size of study. Cream - 200 mg; Yellow - 400 mg; Brown - 600 mg ibuprofen



Headache relief at two hours

Ibuprofen 200 mg versus placebo

Two studies provided data for headache relief at two hours (777 participants). One study used a standard oral formulation (Codispoti 2001) and the other a liquigel formulation (Kellstein 2001).

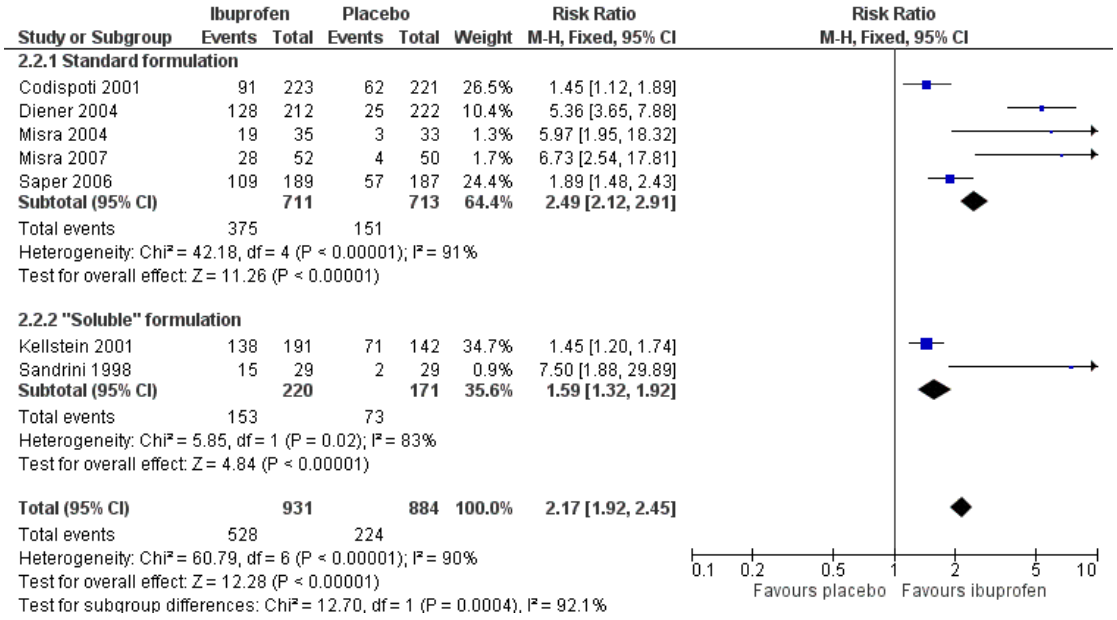
- The proportion of participants experiencing headache relief at two hours with ibuprofen 200 mg was 52% (217/414; range 42% to 64%).
- The proportion of participants experiencing headache relief at two hours with placebo was 37% (133/363; range 28% to 50%).
- The relative benefit of treatment compared to placebo was 1.4 (1.2 to 1.6); the NNT was 6.3 (4.4 to 11) (Analysis 1.2).

Ibuprofen 400 mg versus placebo

Seven studies provided data for headache relief at two hours (1815 participants). Five studies used a standard oral formulation (Codispoti 2001; Diener 2004; Misra 2004; Misra 2007; Saper 2006), one used a liquigel formulation (Kellstein 2001) and one used an ibuprofen-arginine preparation (Sandrini 1998).

- The proportion of attacks with headache relief at two hours with ibuprofen 400 mg was 57% (528/931; range 41% to 72%).
- The proportion of attacks with headache relief at two hours with placebo was 25% (224/884; range 7% to 50%).
- The relative benefit of treatment compared to placebo was 2.2 (1.9 to 2.5); the NNT was 3.2 (2.8 to 3.7) (Analysis 2.2; Figure 4).

Figure 4. Forest plot of comparison: 2 Ibuprofen 400 mg versus placebo, outcome: 2.2 Headache relief at 2 hours.

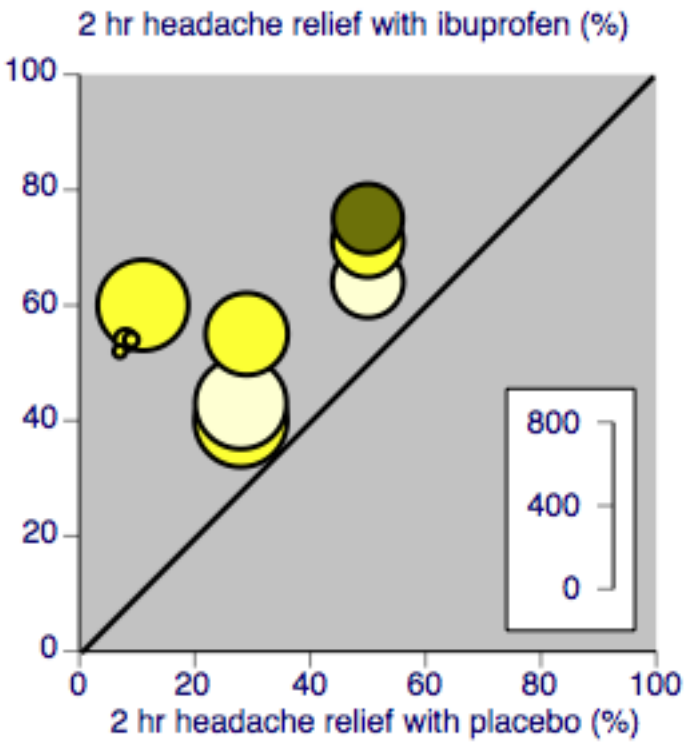


Subgroup analysis for formulation

The two studies using soluble preparations (391 attacks) gave an NNT of 3.7 (2.7 to 5.8), while the five studies using standard preparations (1428 attacks) gave an NNT of 3.2 (2.8 to 3.7). Subgroup analysis comparing these two groups of studies gave z = 0.863, P = 0.390. There was no significant difference between formulations for headache relief at two hours.

A L'Abbé plot for this outcome shows consistency of response with different doses (Figure 5).

Figure 5. L'Abbé plot showing 2-hour headache relief for ibuprofen versus placebo. Size of circle is proportional to size of study. Cream - 200 mg; Yellow - 400 mg; Brown - 600 mg ibuprofen



Subgroup analysis for ibuprofen 400 mg versus ibuprofen 200 mg (all formulations)

Subgroup analysis comparing studies using all formulations of ibuprofen 400 mg and ibuprofen 200 mg for headache relief at two hours gave z = 3.761, P = 0.0002. Ibuprofen 400 mg was significantly better than ibuprofen 200 mg for headache relief at two hours.

Ibuprofen 400 mg versus rofecoxib 25 mg

Two studies provided data for a direct comparison of ibuprofen 400 mg and rofecoxib 25 mg for headache relief at two hours (444 participants, Misra 2004; Saper 2006).

- The proportion of participants experiencing headache relief at two hours with both ibuprofen 400 mg and rofecoxib 25 mg was 57% (128/224; range 54% to 58% and 126/220; range 45% to 59%, respectively).
- The relative benefit of treatment was 1.00 (0.85, 1.17); there was no difference between treatments (Analysis 3.1).

Headache relief at one hour

Ibuprofen 200 mg versus placebo

Two studies provided data for headache relief at one hour (777 participants). One study used a standard oral formulation (Codispoti 2001) and the other a liquigel formulation (Kellstein 2001).

- The proportion of participants experiencing headache relief at one hour with ibuprofen 200 mg was 34% (141/414; range 8% to 41%);
- The proportion of participants experiencing headache relief at one hour with placebo was 23% (83/363; range 21% to 26%);
- The relative benefit of treatment compared to placebo was 1.5 (1.2 to 1.8); the NNT was 8.9 (5.7 to 20) (Analysis 1.3).

Ibuprofen 400 mg versus placebo

Four studies provided data for headache relief at one hour (1269 participants). Two studies used a standard oral formulation (Codispoti 2001; Diener 2004), one used a liquigel formulation (Kellstein 2001) and one used an ibuprofen-arginine preparation (Sandrini 1998).

- The proportion of attacks with headache relief at one hour with ibuprofen 400 mg was 35% (226/655; range 25% to 48%);
- The proportion of attacks with headache relief at one hour with placebo was 18% (108/614; range 0% to 26%);
- The relative benefit of treatment compared to placebo was 1.9 (1.5 to 2.3); the NNT was 5.9 (4.6 to 8.2) (Analysis 2.3).

Subgroup analysis for formulation

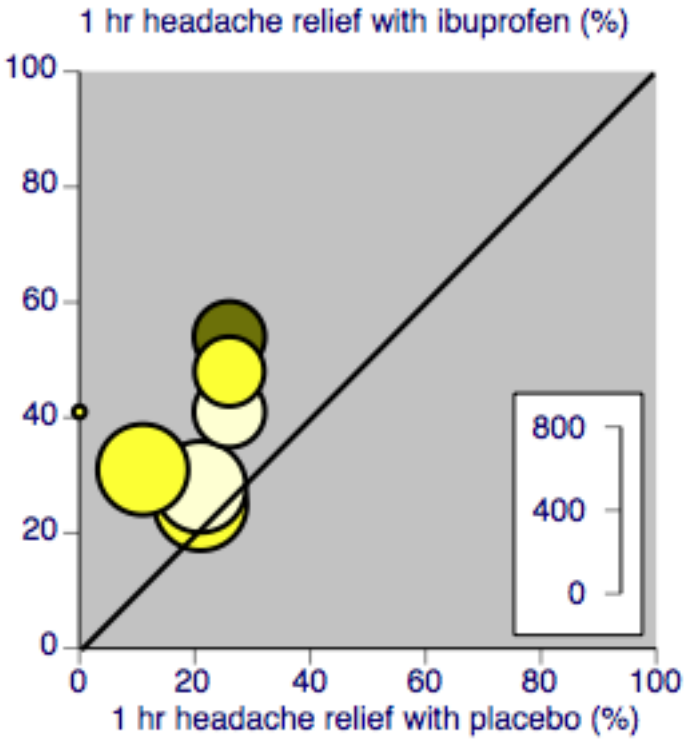
The two studies using soluble preparations (391 attacks) gave an NNT of 3.9 (2.9 to 6.0), while the two studies using standard preparations (878 attacks) gave an NNT of 8.3 (5.7 to 15). Subgroup analysis comparing these two groups of studies gave z = 2.532, P = 0.0114. Soluble formulations were significantly better than standard formulations for headache relief at one hour.

Ibuprofen 600 mg versus placebo

Only one study (Kellstein 2001), using a liquigel formulation, provided data for headache relief at one hour (340 participants): 54% of participants had this outcome with ibuprofen 600 mg, and 26% with placebo.

A L'Abbé plot for this outcome shows consistency of response with different doses (Figure 6).

Figure 6. L'Abbé plot showing 1-hour headache relief for ibuprofen versus placebo. Size of circle is proportional to size of study. Cream - 200 mg; Yellow - 400 mg; Brown - 600 mg ibuprofen



Sustained pain-free at 24 hours

Ibuprofen 400 mg versus placebo

Only one study (Saper 2006) provided data for 24-hour sustained pain-free response (376 participants) using a standard formulation: 18% of participants had this outcome with ibuprofen 400 mg, and 3% with placebo.

Sustained headache relief at 24 hours

Ibuprofen 200 mg versus placebo

Only one study (Kellstein 2001) provided data for 24-hour sustained headache relief (340 participants) using the liquigel formulation: 54% of participants had this outcome with ibuprofen 200 mg, and 35% with placebo.

Ibuprofen 400 mg versus placebo

Four studies provided data for 24-hour sustained headache relief (879 participants). Three studies used a standard oral formulation (Misra 2004; Misra 2007; Saper 2006), and one used a liquigel formulation (Kellstein 2001).

- The proportion of participants achieving 24-hour sustained relief with ibuprofen 400 mg was 45% (208/467; range 31% to 58%).
- The proportion of participants achieving 24-hour sustained relief with placebo was 19% (80/412; range 6% to 35%).
- The relative benefit of treatment compared to placebo was 2.2 (1.8 to 2.7); the NNT was 4.0 (3.2 to 5.2) (Analysis 2.4).

Subgroup analysis for formulation

The three studies using standard preparations (546 participants) gave an NNT of 4.2 (3.3 to 5.8), which was not significantly changed.

Ibuprofen 400 mg versus rofecoxib 25 mg

Two studies provided data for a direct comparison of ibuprofen 400 mg and rofecoxib 25 mg for sustained relief at 24 hours (444 participants, Misra 2004; Saper 2006).

- The proportion of participants experiencing sustained relief with ibuprofen 400 mg was 33% (74/224; range 31 to 43%).
- The proportion of participants experiencing sustained relief with rofecoxib 25 mg was 39% (85/220; range 36% to 39%).
- The relative benefit of ibuprofen compared to rofecoxib was 0.85 (0.66 to 1.1); the NNT was not calculated (Analysis 3.2).

Summary of results A: Pain-free and headache relief

	Studies	Participants/ Attacks	Treatment (%)	Placebo or comparator (%)	RR (95% CI)	NNT (95% CI)	P for difference
Pain-free at 2 hours							
Ibuprofen 200 mg versus placebo	2	777	20	10	2.0 (1.4 to 2.8)	9.7 (6.5 to 18)	
Ibuprofen 400 mg versus placebo	6	2575	26	12	1.9 (1.6 to 2.3)	7.2 (5.9 to 9.2)	
Headache relief at 1 hour							
Ibuprofen 200 mg versus placebo	2	777	34	23	1.5 (1.2 to 1.8)	8.9 (5.7 to 20)	
Ibuprofen 400 mg versus placebo	4	1269	35	18	1.9 (1.5 to 2.3)	5.9 (4.6 to 8.2)	

(*Continued*)

Soluble formulation	2	391	47	22	2.1 (1.6 to 2.9)	3.9 (2.9 to 6.0)	z = 2.532 P = 0.0114
Standard formulation	2	878	28	16	1.8 (1.3 to 2.3)	8.3 (5.7 to 15)	
Headache relief at 2 hours							
Ibuprofen 200 mg versus placebo	2	777	52	37	1.4 (1.2 to 1.6)	6.3 (4.4 to 11)	z = 3.761 P = 0.0002
Ibuprofen 400 mg versus placebo	7	1815	57	25	2.2 (1.9 to 2.5)	3.2 (2.8 to 3.7)	
Soluble formulation	2	391	70	43	1.6 (1.3 to 1.9)	3.7 (2.7 to 5.8)	z = 0.863 P = 0.390
Standard formulation	5	1424	53	21	2.5 (2.1 to 2.9)	3.2 (2.8 to 3.7)	
Ibuprofen 400 mg versus rofecoxib 25 mg	2	444	57	57	1.00 (0.85 to 1.2)	Not calculated	
Sustained headache relief at 24 hours							
Ibuprofen 400 mg versus placebo	4	879	45	19	2.2 (1.8 to 2.7)	4.0 (3.2 to 5.2)	
Ibuprofen 400 mg versus rofecoxib 25 mg	2	444	33	39	0.85 (0.66 to 1.1)	Not calculated	

Subgroup analyses

Different doses of ibuprofen and the effect of formulation (standard versus soluble) have been considered above in the main analysis.

Only one of the included studies used ibuprofen in combination with an antiemetic (intravenous metoclopramide, which was not self-administered; Ellis 1993) and did not report any primary outcome data. All included studies used the oral route of administration for ibuprofen, so no subgroup analyses could be carried out for these criteria.

Sensitivity analysis

All studies scored ≥ 3 out of 5 on the Oxford Quality Score, but a sensitivity analysis was carried out excluding Misra 2004 and Misra 2007 because there was doubt about the effectiveness of their double-blinding, and also because it was not clear how they combined data for multiple attacks.
In no case did exclusion of one or both of these studies significantly change the efficacy estimates. Details for individual outcomes are reported immediately below.

Pain-free at two hours

When Misra 2007 was removed from the analysis of ibuprofen 400 mg versus placebo, the relative benefit was 1.8 (1.5 to 2.2) and the NNT was 7.6 (6.2 to 9.9).

Headache relief at two hours

When Misra 2004 and Misra 2007 were removed from the analysis of ibuprofen 400 mg versus placebo, the relative benefit was 2.0 (1.8 to 2.3) and the NNT was 3.3 (2.9 to 3.9).

Sustained headache relief at 24 hours

When Misra 2004 and Misra 2007 were removed from the analysis of ibuprofen 400 mg versus placebo, the relative benefit was 1.9 (1.5 to 2.3) and the NNT was 4.6 (3.5 to 6.6).

Adverse events

Any adverse event

Ibuprofen 200 mg versus placebo

Two studies (780 participants) provided data for the number of participants experiencing at least one adverse event within 24 hours of medication (Codispoti 2001; Kellstein 2001).

- The proportion of participants experiencing any adverse event with ibuprofen 200 mg was 22% (90/416; range 10% to 33%).
- The proportion of participants experiencing any adverse event with placebo was 28% (101/364; range 13% to 37%).
- The relative risk of treatment compared to placebo was 0.85 (0.67 to 1.1); the NNH was not calculated (Analysis 1.4).

Ibuprofen 400 mg versus placebo

Seven studies (1767 attacks) provided data for the number of participants experiencing at least one adverse event within 24 hours of medication (Codispoti 2001; Diener 2004; Goldstein 2006; Kellstein 2001; Misra 2007; Sandrini 1998; Saper 2006).

- The proportion of participants experiencing any adverse event with ibuprofen 400 mg was 15% (231/1557; range 10% to 35%).
- The proportion of participants experiencing any adverse event with placebo was 19% (206/1079; range 6% to 37%).
- The relative risk of treatment compared to placebo was 0.97 (0.82 to 1.2); the NNH was not calculated (Analysis 2.5).

Specific adverse events

Reporting of specific adverse events was inconsistent; for example, some studies did not report any dichotomous information (e.g., Diener 2004); two reported on the most common drug-related events (Codispoti 2001; Saper 2006); and another reported on severe, drug-related events (Kellstein 2001). Misra 2004 and Misra 2007 reported on 'side effects', which were presumably drug-related adverse events. In addition, studies did not use consistent terms; for example, some studies reported 'gastric discomfort' and others 'dyspepsia', and we have combined these terms for analysis where we considered it reasonable to do so, to generate larger numbers. Where a study did not report a specific type of adverse event, it was not always clear whether that event did not occur at all, or whether it did not occur sufficiently often or with sufficient severity to be reported. This could lead to overestimation of event rates where studies with no events are not included in the analysis. Generally, where reported, rates of specific adverse events, such as nausea, abdominal pain, dyspepsia, dizziness and somnolence, were below 5%, with a few exceptions in individual studies. Nausea rates were high in Codispoti 2001, and abdominal pain was high in Misra 2004 and Misra 2007. These discrepancies may result from differences in the information given to participants about adverse events, and the methods of collection of adverse event data.
Fewer participants reported nausea as an adverse event with ibuprofen 400 mg than with placebo, although the difference was barely significant; this may reflect the active drug reducing a migraine-associated symptom. Significantly more participants experienced abdominal pain with ibuprofen 400 mg than with placebo. Dizziness and somnolence were not significantly different between ibuprofen and placebo (Analysis 2.6). There were insufficient data to analyse any other specific events (Appendix 6).

Serious adverse events

Only three serious adverse events were reported. One participant treated with ibuprofen experienced perforation of a duodenal ulcer after ibuprofen 400 mg, and one experienced renal colic after

buffered aspirin 1000 mg (Diener 2004). Both these events were judged to be possibly causally related to study medication, and both resolved completely. One participant randomised to ibuprofen 400 mg died of sepsis (Saper 2006). The event was judged definitely not related to the study medication, and it was not known whether she actually took the medication.

Withdrawals

Participants withdrawing due to lack of efficacy took rescue medication (see Appendix 7).

Withdrawals due to adverse events were uncommon. Two participants treated with ibuprofen 400 mg and three treated with placebo withdrew because of nausea or vomiting (Codispoti 2001); one participant treated with ibuprofen 400 mg was hospitalised with a perforated duodenal ulcer (see Serious adverse events, above, Diener 2004); and one participant randomised to ibuprofen 400 mg died of sepsis (see Serious adverse events, above, Saper 2006).

A number of participants who were randomised to treatment were not included in efficacy and/or safety analyses, mainly due to protocol violations or lack of any post-baseline data. These exclusions were fairly evenly distributed between treatment groups, and the numbers involved were not likely to have affected results.

DISCUSSION

Summary of main results

This review included nine randomised, double-blind, placebo-controlled studies, with 3364 migraine headaches of moderate to severe intensity treated with ibuprofen 200 mg, 400 mg, and 600 mg, and with placebo. Most studies used standard formulation tablets, but two used soluble formulations (liquigel or arginine salt). Six studies included active comparators, but only rofecoxib 25 mg provided sufficient data for analysis. No studies combined ibuprofen with a self-administered antiemetic. All treated attacks with a single dose of study medication; none examined alternative dosing strategies or regimens.

For the IHS preferred outcome of pain-free at two hours, both ibuprofen 200 mg and 400 mg were better than placebo, giving NNTs of 9.7 and 7.2, respectively, with no significant difference between active treatments; 26% of participants were pain-free at two hours with 400 mg, 20% with 200 mg, and 11% with placebo.

For headache relief at two hours, both ibuprofen 200 mg and 400 mg were significantly better than placebo, with NNTs of 6.3 and 3.2, respectively; 57% of participants had headache relief at two hours with 400 mg, 52% with 200 mg, and 25 to 37% with placebo. The 400 mg dose was significantly better than 200 mg (P = 0.0002). For headache relief at one hour, the NNTs were 8.9 and 5.9 respectively, with no significant difference between doses; 35% of participants were headache-free at two hours with 400 mg, 34% with 200 mg, and 18 to 23% with placebo. Ibuprofen 400 mg was significantly better than placebo for the outcome of 24-hour sustained headache relief, with an NNT of 4; 45% of participants were headache free at two hours with 400 mg, and 19% with placebo. About one in three participants treated with ibuprofen 400 mg experienced headache relief at one hour, just over half experienced relief at two hours, and just under half sustained relief for 24 hours, but only around one in four or one in five were pain-free at two hours.

These results are similar to those found for aspirin 900 mg or 1000 mg in a separate Cochrane review (Kirthi 2013), with ibuprofen 400 mg performing slightly better than aspirin, and ibuprofen 200 mg slightly worse. In that review, NNTs for aspirin 900 mg or 1000 mg alone versus placebo were 8.1, 4.9 and 6.6 for 2-hour pain-free, 2-hour headache relief and 24-hour headache relief, respectively; NNTs for aspirin plus metoclopramide versus placebo were 8.8, 3.3 and 6.2, respectively.

For headache relief at one hour with ibuprofen 400 mg, there was a significant difference between soluble and standard formulations (P = 0.0114), but by two hours the difference was lost. This almost certainly reflects a faster uptake of the soluble formulation resulting in a more rapid effect, but by two hours the standard formulation had 'caught up'.

There was no significant difference between ibuprofen 400 mg and rofecoxib 25 mg for headache relief at two hours or 24-hour headache relief. Rofecoxib has now been withdrawn by the manufacturers, but we chose to retain it in this analysis because rofecoxib 50 mg is known to be an effective analgesic in acute pain (Bulley 2009).

Overall the number of participants experiencing one or more adverse events did not differ between ibuprofen and placebo. Most adverse events were described as mild or moderate, and transient. Significantly more participants reported abdominal pain with ibuprofen 400 mg than with placebo, but dizziness and somnolence did not differ, and there were slightly fewer cases of nausea with ibuprofen 400 mg. Serious adverse events and adverse event withdrawals were uncommon.

Additional analyses (Appendix 7) show that fewer participants needed rescue medication with ibuprofen 200 mg (27%) or 400 mg (38%) than with placebo (40 to 58%; NNTps 7.4 and 4.9).

Participants treated with ibuprofen had better relief of migraine-associated symptoms compared with those treated with placebo. There was a non-significant trend for better relief of nausea, photophobia and phonophobia with ibuprofen 400 mg than 200 mg (NNTs 5 to 8 and 7 to 13, respectively). There were relatively few participants with vomiting. Functional disability was also significantly improved with both doses of ibuprofen (42% to 46% had relief of functional disability) compared to placebo (only 24% to 30% had relief).

Overall completeness and applicability of

evidence

Included participants all had a diagnosis of migraine headaches according to IHS criteria (IHS 1988), except in one study which predated these but used criteria compatible with them (Ellis 1993). Attacks occurred at a frequency of one every two months to eight per month and were of moderate to severe intensity. Only one study specifically recruited participants who had previously experienced some relief with OTC medications, but four excluded participants who usually experienced frequent vomiting with attacks (> 20%) and/or disability requiring bed rest. A variety of methods were used to recruit participants, including attendance at neurology outpatient departments, random-number telephone recruitment, and advertising. The population studied is therefore not likely to be greatly biased towards milder or OTC-responsive individuals, although it may under-represent those with particularly difficult-to-treat headaches. 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 ibuprofen.

The amount of information for active comparators was small, allowing analyses only for comparisons with rofecoxib 25 mg, and even here, 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 did not differ between ibuprofen (any dose) and 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.

We found only one small study (Ellis 1993) investigating the combination of ibuprofen with an antiemetic, and in this case the antiemetic was administered intravenously in hospital, so did not comply with our inclusion criteria for self-administration. Combining aspirin with metoclopramide gives improved headache response at two hours, and better relief of nausea, compared with aspirin alone (Kirthi 2013), and one could expect a similar improvement for ibuprofen. No studies specifically investigated the early use of ibuprofen 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).

The lysine salt of ibuprofen is used in OTC medications targeted specifically at migraine. We found no studies reporting on the efficacy of ibuprofen lysine. In acute postoperative pain, soluble salts of ibuprofen (mainly lysine and arginine salts) produced significantly better efficacy than standard formulations (Derry 2009). While there is no reason to expect that ibuprofen lysine would produce worse results than standard ibuprofen in migraine, and one might expect it to provide similar efficacy to ibuprofen arginine and the liquigel formulation (for which we have data in this review), the absence of studies using the lysine salt is unfortunate.

Quality of the evidence

Included studies were of good methodological quality and validity. Some did not adequately describe the method of randomisation or 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. Two studies (Misra 2004; Misra 2007) described themselves as double-blind, but used treatments that were potentially distinguishable if directly compared. We chose to include these studies, subject to a sensitivity analysis, which did not suggest any problem with the blinding.

Potential biases in the review process

The main area of concern is the small numbers of events used to calculate some results.

We investigated the potential influence of 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 chose a clinically useful level as NNTs of 8 for pain-free at two hours, and 6 for headache relief at two hours. For pain-free at two hours almost 300 participants, and for headache relief at two hours almost 1600 participants, would have to have been involved in unpublished trials with zero treatment effect for the NNT to increase above the specified thresholds. While this quantity of data may exist, it seems unlikely that further studies would overturn the results seen here, although the size of the effect could easily be changed (reduced) by the presence of unpublished data.

Agreements and disagreements with other studies or reviews

A systematic review of interventions for acute migraine with a literature search to 2000 identified no studies using ibuprofen (Oldman 2002). We included two studies published before 2000; one (Ellis 1993) had no data for relief of headache but did provide data for associated symptoms, and the other (Sandrini 1998) reported headache relief, which we were able to use, rather than pain intensity. A more recent systematic review of low-dose ibuprofen for acute migraine headaches (Suthisisang 2007) included five of the nine studies in this review. It did not include the two studies using soluble formulations of ibuprofen (Kellstein 2001; Sandrini

1998), one study published after the search date (Misra 2007), and one other (Ellis 1993), probably because it did not report the primary outcomes. Results for efficacy from that review are in general agreement with this one: we have marginally lower (better) NNTs because of additional studies, and have been able to compare standard tablets with soluble formulations. Additionally this review reports on use of rescue medication, which is a measure of lack of efficacy or inadequate treatment effect, and on functional disability, adverse events and withdrawals.

AUTHORS' CONCLUSIONS

Implications for practice

Ibuprofen is an effective treatment for acute migraine headaches in adults at doses of 200 mg and 400 mg, providing complete headache relief within two hours to 1 in 5 and 1 in 4 individuals taking those doses, respectively; participants in these studies also experienced reduction in pain (about 1 in 2), functional disability and migraine-associated symptoms, such as nausea and photophobia. The 400 mg dose was numerically superior to 200 mg for all efficacy outcomes, but achieved statistical significance only for headache relief at two hours. Soluble formulations gave significantly better results for headache relief than standard tablets at one, but not two hours. No increase in numbers of participants with any adverse event, adverse event withdrawals or serious adverse events was seen with ibuprofen compared to placebo. Ibuprofen 400 mg would seem to be a good first-line therapy for acute migraine headaches in this population.

Implications for research

Further studies are needed to establish the efficacy of the more soluble formulations of ibuprofen, particularly ibuprofen lysine, and of higher doses (600 to 800 mg). Direct comparisons with triptans and other OTC analgesics, such as aspirin and paracetamol 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. Combining ibuprofen with an antiemetic, such as metoclopramide, has the potential to provide better relief of nausea and vomiting, and may also improve headache relief.

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.

The Oxford Pain Research Trust provided institutional support for this update, and editorial support was funded by the International Headache Society.

REFERENCES

References to studies included in this review

Codispoti 2001 *{published data only}*
Codispoti JR, Prior MJ, Fu M, Harte CM, Nelson EB. Efficacy of nonprescription doses of ibuprofen for treating migraine headache. A randomized controlled trial. *Headache* 2001;**41**(7):665–79. DOI: 10.1046/j.1526-4610.2001.041007665.x

Diener 2004 *{published data only}*
Diener HC, Bussone G, de Liano H, Eikermann A, Englert R, Floeter T, et al. The EMSASI Study Group. Placebo-controlled comparison of effervescent acetylsalicylic acid, sumatriptan and ibuprofen in the treatment of migraine attacks. *Cephalalgia* 2004;**24**(11):947–54. DOI: 10.1111/j.1468-2982.2004.00783.x

Ellis 1993 *{published data only}*
Ellis GL, Delaney J, DeHart DA, Owens A. The efficacy of metoclopramide in the treatment of migraine headache. *Annals of Emergency Medicine* 1993;**22**(2):191–5. DOI: 10.1016/S0196-0644(05)80201-X

Goldstein 2006 *{published data only}*
Goldstein J, Silberstein SD, Saper JR, Ryan RE Jr, Lipton RB. Acetaminophen, aspirin, and caffeine in combination versus ibuprofen for acute migraine: results from a multicenter, double-blind, randomized, parallel-group, single-dose, placebo-controlled study. *Headache* 2006;**46**(3):444–53. DOI: 10.1111/j.1526-4610.2006.00376.x

Kellstein 2001 *{published data only}*
Kellstein DE, Lipton RB, Geetha R, Koronkiewicz K, Evans FT, Stewart WF, et al. Evaluation of a novel solubulized formulation of ibuprofen in the treatment of migraine headache: a randomized, double blind, placebo-controlled, dose-ranging study. *Cephalagia* 2001;**20**(4):233–43. DOI: 10.1046/j.1468-2982.2000.00055.x

Misra 2004 *{published data only}*
Misra UK, Jose M, Kalita J. Rofecoxib versus ibuprofen for acute treatment of migraine:a randomised placebo controlled trial. *Postgraduate Medical Journal* 2004;**80**(950):720–3. DOI: 10.1136/pgmj.2003.012393

Misra 2007 *{published data only}*
Misra UK, Kalita J, Yadav RK. Rizatriptan vs. ibuprofen in migraine:a randomised placebo-controlled trial. *Journal of Headache and Pain* 2007;**8**(3):175–9. DOI: 10.1007/s10194-007-0386-7

Sandrini 1998 *{published data only}*
Sandrini G, Franchini S, Lanfranchi S, Granella F, Manzoni GC, Nappi G. Effectiveness of ibuprofen-arginine in the treatment of acute migraine attacks. *International Journal of Clinical Pharmacology Research* 1998;**18**(3):145–51. PUBMED: 9825271]

Saper 2006 *{published data only}*
Saper J, Dahlof C, So Y, Tfelt-Hansen P, Malbecq W, Loeys T, et al. Rofecoxib in the acute treatment of migraine: A randomized controlled clinical trial. *Headache* 2006;**46**(2):264–75. DOI: 10.1111/j.1526-4610.2006.00334.x

References to studies excluded from this review

Havanka 1989 *{published data only}*
Havanka-Kanniainen H. Treatment of acute migraine attack: ibuprofen and placebo compared. *Headache* 1989;**29**(8):507–9.

Kalita 2009 *{published data only}*
Kalita J, Yadav RK, Misra UK. A comparison of migraine patients with and without allodynic symptoms. *Clin J Pain* 2009;**25**(8):696–8.

Kloster 1992 *{published data only}*
Kloster R, Nestvold K, Vilming ST. A double-blind study of ibuprofen versus placebo in the treatment of acute migraine attacks. *Cephalalgia* 1992;**12**(3):169–71.

Nebe 1995 *{published data only}*
Nebe J, Heier H, Diener HC. Low-dose ibuprofen in self-medication of mild to moderate headache: a comparison with acetylsalicylic acid and placebo. *Cephalalgia* 1995;**15**(6):531–5.

Pearce 1983 *{published data only}*
Pearce I, Frank GJ, Pearce JM. Ibuprofen compared with paracetamol in migraine. *The Practioner* 1983;**227**(1377):465–7.

Additional references

Ayzenberg 2012
Ayzenberg I, Katsarava Z, Sborowski A, Chernysh M, Osipova V, Tabeeva G, et al. The prevalence of primary headache disorders in Russia: a countrywide survey. *Cephalalgia* 2012;**32**(5):373–81. DOI: 10.1177/0333102412438977

Bigal 2008
Bigal ME, Serrano D, Reed M, Lipton RB. Chronic migraine in the population: burden, diagnosis, and satisfaction with treatment. *Neurology* 2008;**71**(8):559–66. DOI: 10.1212/01.wnl.0000323925.29520.e7

Bloudek 2012
Bloudek LM, Stokes M, Buse DC, Wilcox TK, Lipton RB, Goadsby PJ, et al. Cost of healthcare for patients with migraine in five European countries: results from the International Burden of Migraine Study (IBMS). *Journal of Headache and Pain* 2012;**13**(5):361–78. DOI: 10.1007/s10194-012-0460-7

Bulley 2009
Bulley S, Derry S, Moore RA, McQuay HJ. Single dose oral rofecoxib for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 4. DOI: 10.1002/14651858.CD004604.pub3

Buse 2011
Buse D, Manack A, Serrano D, Reed M, Varon S, Turkel C, et al. Headache impact of chronic and episodic migraine: results from the American Migraine Prevalence and Prevention study. *Headache* 2012;**52**(1):3–17. DOI: 10.1111/j.1526-4610.2011.02046.x

Collins 1997
Collins SL, Moore RA, McQuay HJ. The visual analogue pain intensity scale: what is moderate pain in millimetres?. *Pain* 1997;**72**(1-2):95–7.

Cook 1995
Cook RJ, Sackett DL. The number needed to treat: a clinically useful measure of treatment effect. *BMJ* 1995;**310**(6977):452–4.

Derry 2009
Derry C, Derry S, Moore RA, McQuay HJ. Single dose oral ibuprofen for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 3. DOI: 10.1002/14651858.CD001548.pub2

Derry 2012b
Derry C, Derry S, Moore A. Sumatriptan (oral route of administration) for acute migraine attacks in adults. *Cochrane Database of Systematic Reviews* 2012;**2**:CD008615. DOI: 10.1002/14651858.CD008615.pub2

Derry 2013
Derry S, Rabbie R, Moore RA. Diclofenac with or without an antiemetic for acute migraine headaches in adults. *Cochrane Database of Systematic Reviews* 2013, Issue 4. DOI: 10.1002/14651858.CD008783.pub3

Derry 2013a
Derry S, Moore RA, McQuay HJ. Paracetamol (acetaminophen) with or without an antiemetic for acute migraine headaches in adults. *Cochrane Database of Systematic Reviews* 2013;**4**:CD008040. DOI: 10.1002/14651858.CD008040.pub3

Diamond 2007
Diamond S, Bigal ME, Silberstein S, Loder E, Reed M, Lipton RB. Patterns of diagnosis and acute and preventive treatment for migraine in the United States: results from the American Migraine Prevalence and Prevention study. *Headache* 2007;**47**(3):355–63. DOI: 10.1111/j.1526-4610.2006.00631.x

Friedman 2005
Friedman BW, Corbo J, Lipton RB, Bijur PE, Esses D, Solorzano C, et al. A trial of metoclopramide vs sumatriptan for the emergency department treatment of

migraines. *Neurology* 2005;**64**(3):463–8. DOI: 10.1212/01.WNL.0000150904.28131.DD

Gendolla 2008
Gendolla A. Early treatment in migraine: how strong is the current evidence?. *Cephalalgia* 2008;**28 Suppl 2**:28–35. DOI: 10.1111/j.1468-2982.2008.01688.x

Hazard 2009
Hazard E, Munakata J, Bigal ME, Rupnow MF, Lipton RB. The burden of migraine in the United States: current and emerging perspectives on disease management and economic analysis. *Value in Health* 2009;**12**(1):55–64. DOI: 10.1111/j.1524-4733.2008.00404.x

Higgins 2011
Higgins JPT, Green S (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Altman DG, Sterne JAC editor(s). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]*. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

IHS 1988
Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. *Cephalalgia* 1988;**8 Suppl 7**:1–96.

IHS 2000
International Headache Society Clinical Trials Subcommittee. Guidelines for controlled trials of drugs in migraine: second edition. *Cephalalgia* 2000;**20**(9):765–86.

IHS 2004
Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 2nd edition. *Cephalalgia* 2004;**24 Suppl 1**:1–160.

Jadad 1996a
Jadad AR, Carroll D, Moore A, McQuay H. Developing a database of published reports of randomised clinical trials in pain research. *Pain* 1996;**66**(2-3):239–46.

Jadad 1996b
Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary?. *Controlled Clinical Trials* 1996;**17**(1):1–12.

Kirthi 2013
Kirthi V, Derry S, Moore RA, McQuay HJ. Aspirin with or without an antiemetic for acute migraine headaches in adults. *Cochrane Database of Systematic Reviews* 2013, Issue 4. DOI: 10.1002/14651858.CD008041.pub3

L'Abbé 1987
L'Abbé KA, Detsky AS, O'Rourke K. Meta-analysis in clinical research. *Annals of Internal Medicine* 1987;**107**(2):224–33.

Leonardi 2005
Leonardi M, Steiner TJ, Scher AT, Lipton RB. The global burden of migraine: measuring disability in headache disorders with WHO's Classification of Functioning, Disability and Health (ICF). *Journal of Headache and Pain* 2005;**6**(6):429–40. DOI: 10.1007/s10194-005-0252-4

Linde 2012
Linde M, Gustavsson A, Stovner LJ, Steiner TJ, Barré J, Katsarava Z, et al. The cost of headache disorders in Europe: the Eurolight project. *European Journal of Neurology* 2012;**19**(5):703–11. DOI: 10.1111/j.1468-1331.2011.03612.x

Lipton 1999
Lipton RB, Stewart WF. Acute migraine therapy: do doctors understand what patients with migraine want from therapy? . *Headache* 1999;**39 Suppl 2**:S20–S26.

Lipton 2007
Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, AMPP Advisory Group, et al. Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology* 2007;**68**(5):343–9. [PUBMED: 17261680]

Lucas 2006
Lucas C, Géraud G, Valade D, Chautard MH, Lantéri-Minet M. Recognition and therapeutic management of migraine in 2004, in France: results of FRAMIG 3, a French nationwide population-based survey. *Headache* 2006;**46**(5):715–25. DOI: 10.1111/j.1526-4610.2006.00430.x

Moore 1998
Moore RA, Gavaghan D, Tramer MR, Collins SL, McQuay HJ. Size is everything - large amounts of information are needed to overcome random effects in estimating direction and magnitude of treatment effects. *Pain* 1998;**78**(3):209–16. DOI: 10.1016/S0304-3959(98)00140-7

Moore 2008
Moore RA, Barden J, Derry S, McQuay HJ. Managing potential publication bias. In: McQuay HJ, Kalso E, Moore RA editor(s). *Systematic Reviews in Pain Research: Methodology Refined*. Seattle: IASP Press, 2008:15–24. [ISBN: 978–0–931092–69–5]

Morris 1995
Morris JA, Gardner MJ. Calculating confidence intervals for relative risk, odds ratios and standardised ratios and rates. In: Gardner MJ, Altman DG editor(s). *Statistics with confidence - confidence intervals and statistical guidelines*. London: British Medical Journal, 1995:50–63.

Munakata 2009
Munakata J, Hazard E, Serrano D, Klingman D, Rupnow MF, Tierce J, et al. Economic burden of transformed migraine: results from the American Migraine Prevalence and Prevention (AMPP) Study. *Headache* 2009;**49**(4):498–508. DOI: 10.1111/j.1526-4610.2009.01369.x

Oldman 2002
Oldman AD, Smith LA, McQuay HJ, Moore RA. Pharmacological treatments for acute migraine: quantitative systematic review. *Pain* 2002;**97**(3):247–57. DOI: 10.1016/S0304-3959(02)00024-6

Radtke 2009
Radtke A, Neuhauser H. Prevalence and burden of headache and migraine in Germany. *Headache* 2009;**49**(1):79–89. DOI: 10.1111/j.1526-4610.2008.01263.x

RevMan 2012 [Computer program]
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012.

Ross-Lee 1983
Ross-Lee LM, Eadie MJ, Heazlewood V, Bochner F, Tyrer JH. Aspirin pharmacokinetics in migraine. The effect of metoclopramide. *European Journal of Clinical Pharmacology* 1983;**24**(6):777–85.

Salazar-Tortolero 2008
Salazar-Tortolero G, Huertas-Campistol A, Vergez-Pinto L, Ramos-Brunet A, Lluch-López J. Metoclopramide as a painkiller for intense migraine headache in emergency departments [Metoclopramida como analgésicoen la cefalea migrañosa intensa en urgencias]. *Revista de Neurologia* 2008;**47**(10):506–8. [PUBMED: 19012253]

Steiner 2013
Steiner TS, Stovner LJ, Birbeck GL. Migraine: the seventh disabler. *Journal of Headache and Pain* 2013;**14**:1. DOI: 10.1186/1129-2377-14-1

Stovner 2010
Stovner LJ, Andree C. Prevalence of headache in Europe: a review for the Eurolight project. *Journal of Headache and Pain* 2010;**11**(4):289–99. DOI: 10.1007/s10194-010-0217-0

Suthisisang 2007
Suthisisang C, Poolsup N, Kittikulsuth W, Pudchakan P, Wiwatpanich P. Efficacy of low-dose ibuprofen in acute migraine treatment: systematic review and meta-analysis. *Annals of Pharmacotherapy* 2007;**41**(11):1782–91. DOI: 10.1345/aph.1K121

Tramèr 1997
Tramèr MR, Reynolds DJM, Moore RA, McQuay HJ. Impact of covert duplicate results on meta-analysis: a case study. *BMJ* 1997;**315**(7109):635–9.

Victor 2010
Victor TW, Hu X, Campbell JC, Buse DC, Lipton RB. Migraine prevalence by age and sex in the United States: a life-span study. *Cephalalgia* 2010;**30**(9):1065–72.

Volans 1974
Volans GN. Absorption of effervescent aspirin during migraine. *British Medical Journal* 1974;**4**(5939):265–8.

Volans 1975
Volans GN. The effect of metoclopramide on the absorption of effervescent aspirin in migraine. *British Journal of Clinical Pharmacology* 1975;**2**(1):57–63.

Vos 2012
Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;**380**(9859):2163–96. DOI: 1016/S0140-6736(12)61729-2

Yu 2012
Yu S, Liu R, Zhao G, Yang X, Qiao X, Feng J, et al. The prevalence and burden of primary headaches in China: a population-based door-to-door survey. *Headache* 2012;**52**(4):582–91. DOI: 10.1111/j.1526-4610.2011.02061.x

References to other published versions of this review

Rabbie 2010
Rabbie R, Derry S, Moore RA, McQuay HJ. Ibuprofen with or without an antiemetic for acute migraine headaches in adults. *Cochrane Database of Systematic Reviews* 2010, Issue 10. DOI: 10.1002/14651858.CD008039.pub2

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Codispoti 2001

Methods	Multicentre, randomised, double-blind, placebo-controlled, parallel-group. Single oral dose Medication taken when migraine of moderate or severe intensity Assessments at 0, 0.5, 1, 1.5, 2, 3, 4, 5, and 6 hours If pain not controlled, participants asked to wait 2 hours before taking rescue medication (of participant's choice)
Participants	Migraine with/without aura (IHS 1988) of at least moderate severity. History: 0.5 to 6 episodes/month in the year before study entry Excluded participants with > 50% episodes requiring bedrest or > 20% including vomiting Prophylactic medication continued unchanged, if stable N = 660 M 104, F 556 Mean age 39 years History of aura: 27%
Interventions	Ibuprofen 200 mg, n = 216 Ibuprofen 400 mg, n = 223 Placebo, n = 221
Outcomes	Pain-free at 2 hours Headache relief at 1 and 2 hours Use of rescue medication Presence of nausea, vomiting, photophobia, phonophobia Functional disability Adverse events Withdrawals
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 randomization code"
Allocation concealment (selection bias)	Low risk	"unopened treatment-blinding tear-off portion of winged label was affixed to the patient's case report form"

Codispoti 2001 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	All participants "received a blister card containing two tablets that were identical in colour, size, and shape"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs described
Study size	Low risk	> 200 participants per treatment group

Diener 2004

Methods	Multicentre, randomised, double-blind (double-dummy), placebo-controlled, three-period, cross-over. Single oral dose of each treatment for each of three migraine attacks, with at least 48 hours between consecutive treatments Medication taken within 6 hours of onset, when migraine of moderate or severe intensity, and not improving Assessments at 0, 0.5, 1, 1.5, 2, and 24 hours If pain not controlled, participants asked to wait 2 hours before taking rescue medication (of participant's choice - 12 hours if triptan or ergot)
Participants	Migraine with or without aura (IHS 1988). History: 1 to 6 attacks/month in previous year N = 312 (cross-over trial, 882 attacks) M 59, F 253 Mean age 38 years History of aura: 21%
Interventions	Ibuprofen 400 mg, n = 212 ASA 2 x 500 mg, n = 222 Sumatriptan 50 mg, n = 226 Placebo, n = 222
Outcomes	Pain-free at 2 hours Headache relief at 1 and 2 hours Use of rescue medication Presence of vomiting, photophobia, phonophobia Adverse events Withdrawals
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 randomization code"

Diener 2004 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"double-dummy" method with "matching placebo" for each treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs described
Study size	Low risk	> 200 participants per treatment group

Ellis 1993

Methods	Randomised, double-blind, placebo-controlled, parallel-group. Single oral dose of ibuprofen with or without intravenous metoclopramide Assessments at 0, 0.5 and 1 hour If pain not controlled, participants asked to wait 1 hour before taking rescue medication
Participants	Migraine (predates, but consistent with IHS criteria), presenting at hospital emergency department N = 40 No information on mean age, sex of population Median baseline pain ≥ 8/10 History of aura: not reported
Interventions	Ibuprofen 600 mg (oral) + placebo (IV), n = 10 Placebo (oral) + placebo (IV), n = 10 Ibuprofen 600 mg (oral) + metoclopramide 1 mg IV, n = 10 Placebo (oral) + metoclopramide 1 mg IV, n = 10
Outcomes	Use of rescue medication at 1 hour
Notes	Oxford Quality Score: R1, DB2, W0. 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	Low risk	"identically-appearing placebo"

Ellis 1993 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs described
Study size	High risk	< 50 participants per treatment group

Goldstein 2006

Methods	Multicentre, randomised, double-blind (double-dummy), placebo-controlled, parallel-group. Single oral dose Medication taken when migraine of moderate or severe intensity Assessments at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, and 4 hours If pain not controlled, participants asked to wait 2 hours before taking rescue medication (of participant's choice)
Participants	Migraine with and without aura (IHS 1988). History: attack at least once every 2 months during past year. Untreated attacks ≥ moderate severity N = 1559 M 306, F 1249 Mean age 38 years History of aura: 21%
Interventions	Ibuprofen 2 x 200 mg, n = 669 Paracetamol + aspirin + caffeine 2 x 250/250/65 mg, n = 669 Placebo, n = 221
Outcomes	Pain-free at 2 hours Presence of nausea, vomiting, photophobia, phonophobia Adverse events Withdrawals
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 method
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs described

Goldstein 2006 (*Continued*)

Study size	Low risk	> 200 participants per treatment group

Kellstein 2001

Methods	Multicentre, randomised, double-blind, placebo-controlled, parallel-group. Single oral dose Medication taken when migraine of moderate or severe intensity Assessments at 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, and 24 hours Rescue medication allowed, but no details reported
Participants	Migraine with/without aura (IHS 1988). At least 12-month history of migraine with/without aura, average frequency of 0.5 to 8 attacks/month in the previous year. Untreated attacks ≥ moderate severity. Previous experience of some relief from OTC analgesics Excluded participants with headaches that were usually severely disabling or incapacitating, or ≥ 20% accompanied by vomiting N = 729 M 179, F 550 Mean age 37 years (35 participants were 12 to 19 years) History of aura: 12%
Interventions	Ibuprofen liquigel 200 mg, n = 198 Ibuprofen liquigel 400 mg, n = 191 Ibuprofen liquigel 600 mg, n = 198 Placebo, n = 142
Outcomes	Pain-free at 2 hours Headache relief at 1 and 2 hours 24-hour sustained relief Use of rescue medication Presence of nausea, photophobia, phonophobia Functional disability Adverse events Withdrawals
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	"matching placebo"

Kellstein 2001 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs described
Study size	Unclear risk	50 to 200 participants per treatment group

Misra 2004

Methods	Randomised, double-blind, placebo-controlled, parallel-group. Single oral dose/attack (≥ 2 attacks treated) Medication taken when migraine of moderate or severe intensity Assessments at 0, 2, and 24 hours If moderate or severe headache persisted after 2 hours, rescue medication allowed (sumatriptan 100 mg or piroxicam 20 mg)
Participants	Migraine with and without aura (IHS 1988). History: at least 12-month history of migraine with/without aura, no more than 6 attacks/month. Untreated attacks ≥ moderate severity Excluded participants with headaches usually needing bedrest, or ≥ 20% accompanied by vomiting N = 124 (101 analysed) M 18, F 83 Mean age 32 years History of aura: not reported
Interventions	Ibuprofen 400 mg, n = 35 Rofecoxib 25 mg, n = 33 Placebo, n = 33
Outcomes	Headache relief at 2 hours 24-hour sustained relief Use of rescue medication Adverse events Withdrawals
Notes	Oxford Quality Score: R2, DB1, W1. Total 4 Note exclusions >10% lost to follow-up Note: headache relief not specifically defined

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"random number tables"
Allocation concealment (selection bias)	Unclear risk	Randomisation done by one investigator and responses evaluated by the other, but no details about method of concealment

Misra 2004 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Tablets had identical packets, but were not identical in appearance
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	18.5% lost to follow-up without adequate explanation
Study size	High risk	< 50 participants per treatment group

Misra 2007

Methods	Randomised, double-blind, placebo-controlled, parallel-group. Single oral dose/attack (≥ 2 attacks treated) Medication taken when migraine of moderate or severe intensity Assessments at 0, 2, and 24 hours If moderate or severe headache persisted after 2 hours, rescue medication allowed (piroxicam 20 mg)
Participants	Migraine (IHS 1988). History: ≤ 8 attacks/month. Untreated attacks ≥ moderate severity Excluded participants with headaches associated with recurrent vomiting N = 155 analysed M 59, F 106 Mean age 30 years History of aura: not reported
Interventions	Ibuprofen 400 mg, n = 52 Rizatriptan 10 mg, n = 53 Placebo, n = 50
Outcomes	Pain-free at 2 hours Headache relief at 2 hours 24-hour sustained relief Use of rescue medication Adverse events Withdrawals
Notes	Oxford Quality Score: R2, DB1, W1 Note: headache relief not specifically defined, and may be reduction from moderate or severe by two grades (Kalita 2009), which is not quite the same as reduction to mild or none

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"computer-generated random numbers"

Misra 2007 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Randomisation done by one investigator and responses evaluated by the other, but no details about method of concealment
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Medication "provided in identical packets"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs described
Study size	Unclear risk	50 to 200 participants per treatment group

Sandrini 1998

Methods	DB, cross-over, double-dummy trial Two centre, randomised, double-blind, placebo-controlled, cross-over. Single oral dose of each treatment for each of two migraine attacks - time between consecutive treated attacks not specified Medication taken when pain was ≥ 60 mm Assessments at 0, 0.25, 0.5, 0.75, 1, 2, 4, and 6 hours If pain not controlled, participants asked to wait 2 hours before taking rescue medication
Participants	Migraine headache (IHS 1988). History: ≥ 2 months, without aura, 2 to 6 headache episodes/month N = 34 (29 analysed for efficacy) M 8, F 26 Mean age 34 years
Interventions	Ibuprofen arginine 400 mg, n = 34 Placebo, n = 34
Outcomes	Headache relief at 1 and 2 hours Use of rescue medication Adverse events Withdrawas
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

Sandrini 1998 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	"identical sachets"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Completer analysis for efficacy, but adequate reasons given
Study size	High risk	< 50 participants per treatment group

Saper 2006

Methods	Multicentre, randomised, double-blind, triple-dummy, placebo- and active-controlled, parallel-group. Single oral dose, and extension phase Medication taken when migraine of moderate or severe intensity, and not resolving spontaneously Assessments at 0, 2, and 24 hours If pain not controlled, participants asked to wait 2 hours before taking rescue medication
Participants	Migraine with and without aura (IHS 1988). History: 1 to 8 migraine attacks/month in the 6 months before enrolment N = 783 M 108, F 675 Mean age 40 years History of aura: 12% 32 participants took medication but were excluded from efficacy analyses - probably due to protocol violations or lack of post-baseline data
Interventions	Ibuprofen 400 mg, n = 199 (189 analysed for efficacy) Rofecoxib 25 mg, n = 194 (187 analysed for efficacy) Rofecoxib 50 mg, n = 196 (188 analysed for efficacy) Placebo, n = 194 (187 analysed for efficacy)
Outcomes	Pain-free at 2 hours Headache relief at 2 hours Use of rescue medication Presence of nausea, vomiting, photophobia, phonophobia Functional disability Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Saper 2006 (*Continued*)

Random sequence generation (selection bias)	Low risk	"computer generated randomization schedule"
Allocation concealment (selection bias)	Low risk	Remote allocation
Blinding (performance bias and detection bias) All outcomes	Low risk	Placebo tablets visually matched the three active treatments
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	≤ 5% drop-outs in each group, with no reasons given
Study size	Unclear risk	50 to 200 participants per treatment group

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

Study	Reason for exclusion
Havanka 1989	33% of ibuprofen and 7% of placebo treatment arms had mild headaches
Kalita 2009	Probably mostly the same population as in Misra 2007. Primary analysis according to presence or not of allodynic symptoms
Kloster 1992	No usable data
Nebe 1995	Mixed tension-type and migraine headaches
Pearce 1983	No usable data

DATA AND ANALYSES

Comparison 1. Ibuprofen 200 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain-free at 2 hours	2	777	Risk Ratio (M-H, Fixed, 95% CI)	1.96 [1.36, 2.81]
2 Headache relief at 2 hours	2	777	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [1.17, 1.61]
3 Headache relief at 1 hour	2	777	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [1.15, 1.83]
4 Any adverse event within 24 hours	2	780	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.67, 1.08]
5 Participants using rescue medication	2	777	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.58, 0.86]
6 Relief of associated symptoms at 2 h	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Nausea	2	429	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [1.06, 1.67]
6.2 Photophobia	2	751	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [1.05, 1.85]
6.3 Phonophobia	2	724	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [1.08, 1.82]
7 Relief of functional disability at 2 hours	2	757	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [1.18, 1.66]

Comparison 2. Ibuprofen 400 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain-free at 2 hours	6	2575	Risk Ratio (M-H, Fixed, 95% CI)	1.91 [1.60, 2.28]
2 Headache relief at 2 hours	7	1815	Risk Ratio (M-H, Fixed, 95% CI)	2.17 [1.92, 2.45]
2.1 Standard formulation	5	1424	Risk Ratio (M-H, Fixed, 95% CI)	2.49 [2.12, 2.91]
2.2 “Soluble” formulation	2	391	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [1.32, 1.92]
3 Headache relief at 1 hour	4	1269	Risk Ratio (M-H, Fixed, 95% CI)	1.89 [1.54, 2.30]
3.1 Standard formulation	2	878	Risk Ratio (M-H, Fixed, 95% CI)	1.75 [1.34, 2.27]
3.2 “Soluble” formulation	2	391	Risk Ratio (M-H, Fixed, 95% CI)	2.12 [1.55, 2.89]
4 Sustained headache relief over 24 hours	4	879	Risk Ratio (M-H, Fixed, 95% CI)	2.17 [1.76, 2.69]
5 Any adverse event within 24 hours	7	2656	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.82, 1.15]
6 Specific adverse events	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Nausea	7	2297	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.54, 1.00]
6.2 Abdominal pain	6	2230	Risk Ratio (M-H, Fixed, 95% CI)	2.36 [1.12, 4.96]
6.3 Dizziness	3	1615	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.46, 2.22]
6.4 Somnolence	4	1717	Risk Ratio (M-H, Fixed, 95% CI)	2.53 [0.79, 8.17]
7 Participants using rescue medication	7	1815	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.61, 0.74]
8 Relief of associated symptoms at 2 h	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

8.1 Nausea	3	634	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [1.27, 1.86]
8.2 Vomiting	2	93	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [1.21, 1.92]
8.3 Photophobia	4	1328	Risk Ratio (M-H, Fixed, 95% CI)	1.51 [1.29, 1.77]
8.4 Phonophobia	4	1261	Risk Ratio (M-H, Fixed, 95% CI)	1.63 [1.39, 1.90]
9 Relief of functional disability at 2 hours	3	1114	Risk Ratio (M-H, Fixed, 95% CI)	1.61 [1.38, 1.89]

Comparison 3. Ibuprofen 400 mg versus rofecoxib 25 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Headache relief at 2 hours	2	444	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.85, 1.17]
2 Sustained headache relief over 24 hours	2	444	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.66, 1.10]
3 Participants using rescue medication	2	444	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.95, 1.38]

Comparison 4. Ibuprofen 600 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain-free at 2 hours	1	340	Risk Ratio (M-H, Fixed, 95% CI)	2.19 [1.37, 3.51]
2 Headache relief at 2 hours	1	340	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [1.19, 1.73]

Analysis 1.1. Comparison 1 Ibuprofen 200 mg versus placebo, Outcome 1 Pain-free at 2 hours.

Review: Ibuprofen with or without an antiemetic for acute migraine headaches in adults

Comparison: 1 Ibuprofen 200 mg versus placebo

Outcome: 1 Pain-free at 2 hours

Study or subgroup	Ibuprofen n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Codispoti 2001	34/216	17/221		43.2 %	2.05 [1.18, 3.55]
Kellstein 2001	50/198	19/142		56.8 %	1.89 [1.17, 3.06]
Total (95% CI)	**414**	**363**		**100.0 %**	**1.96 [1.36, 2.81]**

Total events: 84 (Ibuprofen), 36 (Placebo)

Heterogeneity: Chi^2 = 0.05, df = 1 (P = 0.83); I^2 =0.0%

Test for overall effect: Z = 3.62 (P = 0.00029)

Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Ibuprofen 200 mg versus placebo, Outcome 2 Headache relief at 2 hours.

Review: Ibuprofen with or without an antiemetic for acute migraine headaches in adults

Comparison: 1 Ibuprofen 200 mg versus placebo

Outcome: 2 Headache relief at 2 hours

Study or subgroup	Ibuprofen n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Codispoti 2001	90/216	62/221		42.6 %	1.49 [1.14, 1.93]
Kellstein 2001	127/198	71/142		57.4 %	1.28 [1.06, 1.56]
Total (95% CI)	**414**	**363**		**100.0 %**	**1.37 [1.17, 1.61]**

Total events: 217 (Ibuprofen), 133 (Placebo)

Heterogeneity: Chi^2 = 0.80, df = 1 (P = 0.37); I^2 =0.0%

Test for overall effect: Z = 3.86 (P = 0.00011)

Test for subgroup differences: Not applicable

Analysis 1.3. Comparison 1 Ibuprofen 200 mg versus placebo, Outcome 3 Headache relief at 1 hour.

Review: Ibuprofen with or without an antiemetic for acute migraine headaches in adults

Comparison: 1 Ibuprofen 200 mg versus placebo

Outcome: 3 Headache relief at 1 hour

Study or subgroup	Ibuprofen n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Codispoti 2001	60/216	46/221		51.3 %	1.33 [0.95, 1.87]
Kellstein 2001	81/198	37/142		48.7 %	1.57 [1.14, 2.17]
Total (95% CI)	**414**	**363**		**100.0 %**	**1.45 [1.15, 1.83]**

Total events: 141 (Ibuprofen), 83 (Placebo)

Heterogeneity: $Chi^2 = 0.47$, df = 1 (P = 0.49); $I^2 = 0.0\%$

Test for overall effect: Z = 3.12 (P = 0.0018)

Test for subgroup differences: Not applicable

Analysis 1.4. Comparison 1 Ibuprofen 200 mg versus placebo, Outcome 4 Any adverse event within 24 hours.

Review: Ibuprofen with or without an antiemetic for acute migraine headaches in adults

Comparison: 1 Ibuprofen 200 mg versus placebo

Outcome: 4 Any adverse event within 24 hours

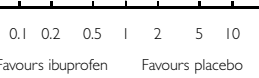
Study or subgroup	Ibuprofen n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Codispoti 2001	71/216	82/221		78.5 %	0.89 [0.69, 1.14]
Kellstein 2001	19/200	19/143		21.5 %	0.72 [0.39, 1.30]
Total (95% CI)	**416**	**364**		**100.0 %**	**0.85 [0.67, 1.08]**

Total events: 90 (Ibuprofen), 101 (Placebo)

Heterogeneity: $Chi^2 = 0.42$, df = 1 (P = 0.52); $I^2 = 0.0\%$

Test for overall effect: Z = 1.35 (P = 0.18)

Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1 Ibuprofen 200 mg versus placebo, Outcome 5 Participants using rescue medication.

Review: Ibuprofen with or without an antiemetic for acute migraine headaches in adults

Comparison: 1 Ibuprofen 200 mg versus placebo

Outcome: 5 Participants using rescue medication

Study or subgroup	Ibuprofen n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Codispoti 2001	79/216	104/221		67.2 %	0.78 [0.62, 0.97]
Kellstein 2001	33/198	43/142		32.8 %	0.55 [0.37, 0.82]
Total (95% CI)	**414**	**363**		**100.0 %**	**0.70 [0.58, 0.86]**

Total events: 112 (Ibuprofen), 147 (Placebo)

Heterogeneity: $Chi^2 = 2.21$, df = 1 (P = 0.14); $I^2 = 55\%$

Test for overall effect: Z = 3.52 (P = 0.00044)

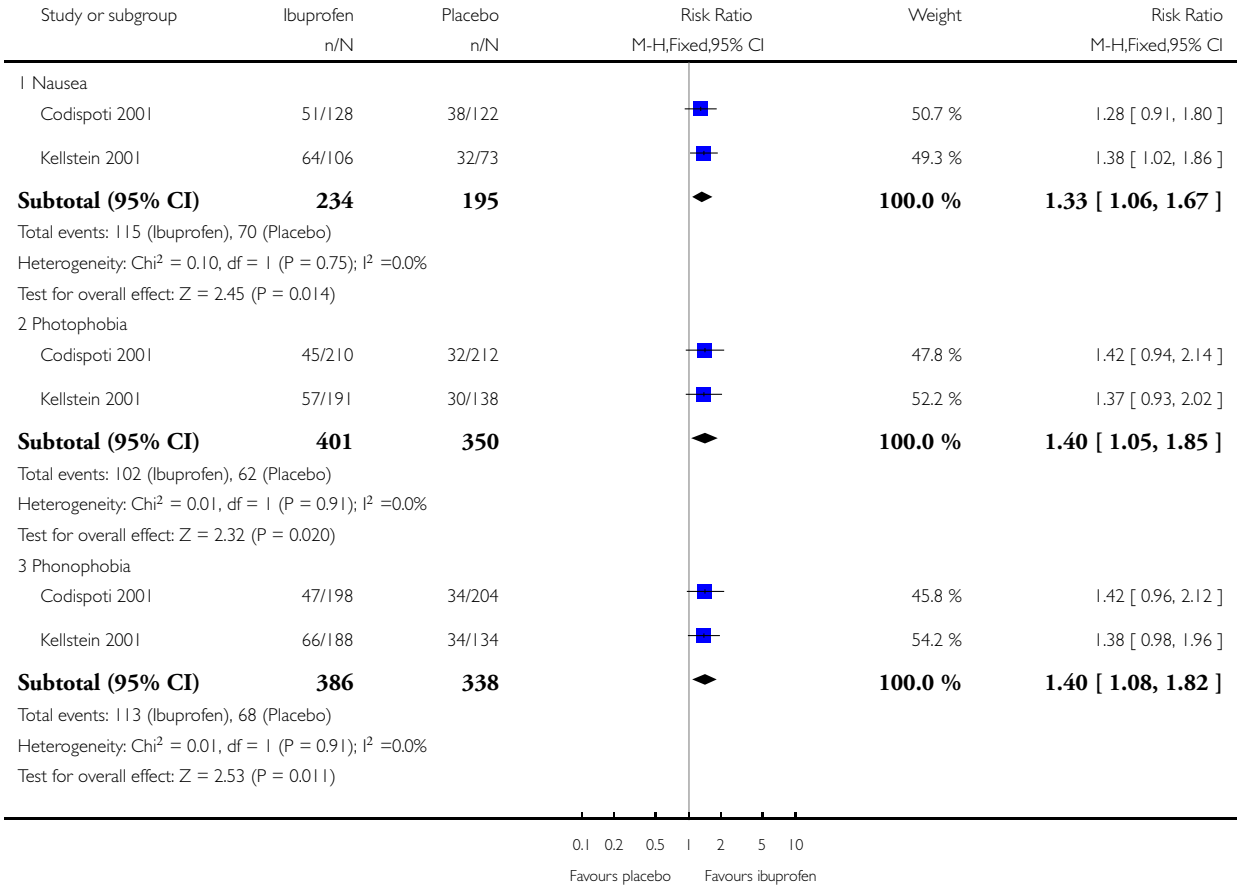
Test for subgroup differences: Not applicable

Analysis 1.6. Comparison 1 Ibuprofen 200 mg versus placebo, Outcome 6 Relief of associated symptoms at 2 h.

Review: Ibuprofen with or without an antiemetic for acute migraine headaches in adults

Comparison: 1 Ibuprofen 200 mg versus placebo

Outcome: 6 Relief of associated symptoms at 2 h



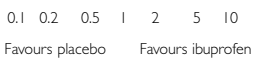
Analysis 1.7. Comparison 1 Ibuprofen 200 mg versus placebo, Outcome 7 Relief of functional disability at 2 hours.

Review: Ibuprofen with or without an antiemetic for acute migraine headaches in adults

Comparison: 1 Ibuprofen 200 mg versus placebo

Outcome: 7 Relief of functional disability at 2 hours

Study or subgroup	Ibuprofen n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Codispoti 2001	44/209	27/210		23.1 %	1.64 [1.06, 2.54]
Kellstein 2001 (1)	143/197	77/141		76.9 %	1.33 [1.12, 1.58]
Total (95% CI)	**406**	**351**		**100.0 %**	**1.40 [1.18, 1.66]**
Total events: 187 (Ibuprofen), 104 (Placebo)					
Heterogeneity: Chi^2 = 0.84, df = 1 (P = 0.36); I^2 =0.0%					
Test for overall effect: Z = 3.88 (P = 0.00010)					
Test for subgroup differences: Not applicable					



(1) Reduced to none or mild

Analysis 2.1. Comparison 2 Ibuprofen 400 mg versus placebo, Outcome 1 Pain-free at 2 hours.

Review: Ibuprofen with or without an antiemetic for acute migraine headaches in adults

Comparison: 2 Ibuprofen 400 mg versus placebo

Outcome: 1 Pain-free at 2 hours

Study or subgroup	Ibuprofen n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Codispoti 2001	31/223	17/221		10.9 %	1.81 [1.03, 3.17]
Diener 2004	70/212	28/222		17.4 %	2.62 [1.76, 3.89]
Goldstein 2006	186/666	53/220		50.8 %	1.16 [0.89, 1.51]
Kellstein 2001	53/191	19/142		13.9 %	2.07 [1.29, 3.34]
Misra 2007	16/52	1/50		0.6 %	15.38 [2.12, 111.72]
Saper 2006	45/189	10/187		6.4 %	4.45 [2.31, 8.57]
Total (95% CI)	**1533**	**1042**		**100.0 %**	**1.91 [1.60, 2.28]**

Total events: 401 (Ibuprofen), 128 (Placebo)

Heterogeneity: Chi^2 = 27.00, df = 5 (P = 0.00006); I^2 =81%

Test for overall effect: Z = 7.22 (P < 0.00001)

Test for subgroup differences: Not applicable

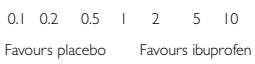
Analysis 2.2. Comparison 2 Ibuprofen 400 mg versus placebo, Outcome 2 Headache relief at 2 hours.

Review: Ibuprofen with or without an antiemetic for acute migraine headaches in adults

Comparison: 2 Ibuprofen 400 mg versus placebo

Outcome: 2 Headache relief at 2 hours

Study or subgroup	Ibuprofen n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Standard formulation					
Codispoti 2001	91/223	62/221		26.5 %	1.45 [1.12, 1.89]
Diener 2004	128/212	25/222		10.4 %	5.36 [3.65, 7.88]
Misra 2004	19/35	3/33		1.3 %	5.97 [1.95, 18.32]
Misra 2007	28/52	4/50		1.7 %	6.73 [2.54, 17.81]
Saper 2006	109/189	57/187		24.4 %	1.89 [1.48, 2.43]
Subtotal (95% CI)	**711**	**713**		**64.4 %**	**2.49 [2.12, 2.91]**
Total events: 375 (Ibuprofen), 151 (Placebo)					
Heterogeneity: Chi^2 = 42.18, df = 4 (P<0.00001); I^2 =91%					
Test for overall effect: Z = 11.26 (P < 0.00001)					
2 "Soluble" formulation					
Kellstein 2001	138/191	71/142		34.7 %	1.45 [1.20, 1.74]
Sandrini 1998	15/29	2/29		0.9 %	7.50 [1.88, 29.89]
Subtotal (95% CI)	**220**	**171**		**35.6 %**	**1.59 [1.32, 1.92]**
Total events: 153 (Ibuprofen), 73 (Placebo)					
Heterogeneity: Chi^2 = 5.85, df = 1 (P = 0.02); I^2 =83%					
Test for overall effect: Z = 4.84 (P < 0.00001)					
Total (95% CI)	**931**	**884**		**100.0 %**	**2.17 [1.92, 2.45]**
Total events: 528 (Ibuprofen), 224 (Placebo)					
Heterogeneity: Chi^2 = 60.79, df = 6 (P<0.00001); I^2 =90%					
Test for overall effect: Z = 12.28 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 12.70, df = 1 (P = 0.00), I^2 =92%					



Analysis 2.3. Comparison 2 Ibuprofen 400 mg versus placebo, Outcome 3 Headache relief at 1 hour.

Review: Ibuprofen with or without an antiemetic for acute migraine headaches in adults

Comparison: 2 Ibuprofen 400 mg versus placebo

Outcome: 3 Headache relief at 1 hour

Study or subgroup	Ibuprofen n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Standard formulation					
Codispoti 2001	56/223	46/221		40.7 %	1.21 [0.86, 1.70]
Diener 2004	66/212	25/222		21.5 %	2.76 [1.82, 4.21]
Subtotal (95% CI)	**435**	**443**		**62.2 %**	**1.75 [1.34, 2.27]**
Total events: 122 (Ibuprofen), 71 (Placebo)					
Heterogeneity: Chi^2 = 9.06, df = 1 (P = 0.003); I^2 =89%					
Test for overall effect: Z = 4.18 (P = 0.000029)					
2 "Soluble" formulation					
Kellstein 2001	92/191	37/142		37.4 %	1.85 [1.35, 2.53]
Sandrini 1998	12/29	0/29		0.4 %	25.00 [1.55, 403.39]
Subtotal (95% CI)	**220**	**171**		**37.8 %**	**2.12 [1.55, 2.89]**
Total events: 104 (Ibuprofen), 37 (Placebo)					
Heterogeneity: Chi^2 = 3.75, df = 1 (P = 0.05); I^2 =73%					
Test for overall effect: Z = 4.74 (P < 0.00001)					
Total (95% CI)	**655**	**614**		**100.0 %**	**1.89 [1.54, 2.30]**
Total events: 226 (Ibuprofen), 108 (Placebo)					
Heterogeneity: Chi^2 = 13.04, df = 3 (P = 0.005); I^2 =77%					
Test for overall effect: Z = 6.23 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 0.88, df = 1 (P = 0.35), I^2 =0.0%					

Analysis 2.4. Comparison 2 Ibuprofen 400 mg versus placebo, Outcome 4 Sustained headache relief over 24 hours.

Review: Ibuprofen with or without an antiemetic for acute migraine headaches in adults

Comparison: 2 Ibuprofen 400 mg versus placebo

Outcome: 4 Sustained headache relief over 24 hours

Study or subgroup	Ibuprofen n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kellstein 2001	111/191	50/142		65.5 %	1.65 [1.28, 2.13]
Misra 2004	15/35	2/33		2.4 %	7.07 [1.75, 28.58]
Misra 2007	23/52	3/50		3.5 %	7.37 [2.36, 23.02]
Saper 2006	59/189	25/187		28.7 %	2.34 [1.53, 3.56]
Total (95% CI)	**467**	**412**		**100.0 %**	**2.17 [1.76, 2.69]**
Total events: 208 (Ibuprofen), 80 (Placebo)					
Heterogeneity: Chi^2 = 11.80, df = 3 (P = 0.01); I^2 =75%					
Test for overall effect: Z = 7.14 (P < 0.00001)					
Test for subgroup differences: Not applicable					

Analysis 2.5. Comparison 2 Ibuprofen 400 mg versus placebo, Outcome 5 Any adverse event within 24 hours.

Review: Ibuprofen with or without an antiemetic for acute migraine headaches in adults

Comparison: 2 Ibuprofen 400 mg versus placebo

Outcome: 5 Any adverse event within 24 hours

Study or subgroup	Ibuprofen n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Codispoti 2001	77/223	82/221		38.3 %	0.93 [0.73, 1.19]
Diener 2004	27/212	32/222		14.5 %	0.88 [0.55, 1.42]
Goldstein 2006	34/669	12/220		8.4 %	0.93 [0.49, 1.77]
Kellstein 2001	26/193	19/143		10.1 %	1.01 [0.58, 1.76]
Misra 2007	8/52	3/50		1.4 %	2.56 [0.72, 9.12]
Sandrini 1998	3/29	4/29		1.9 %	0.75 [0.18, 3.06]
Saper 2006	56/199	54/194		25.4 %	1.01 [0.74, 1.39]
Total (95% CI)	**1577**	**1079**		**100.0 %**	**0.97 [0.82, 1.15]**

Total events: 231 (Ibuprofen), 206 (Placebo)

Heterogeneity: $Chi^2 = 2.75$, df = 6 (P = 0.84); $I^2 = 0.0\%$

Test for overall effect: Z = 0.33 (P = 0.74)

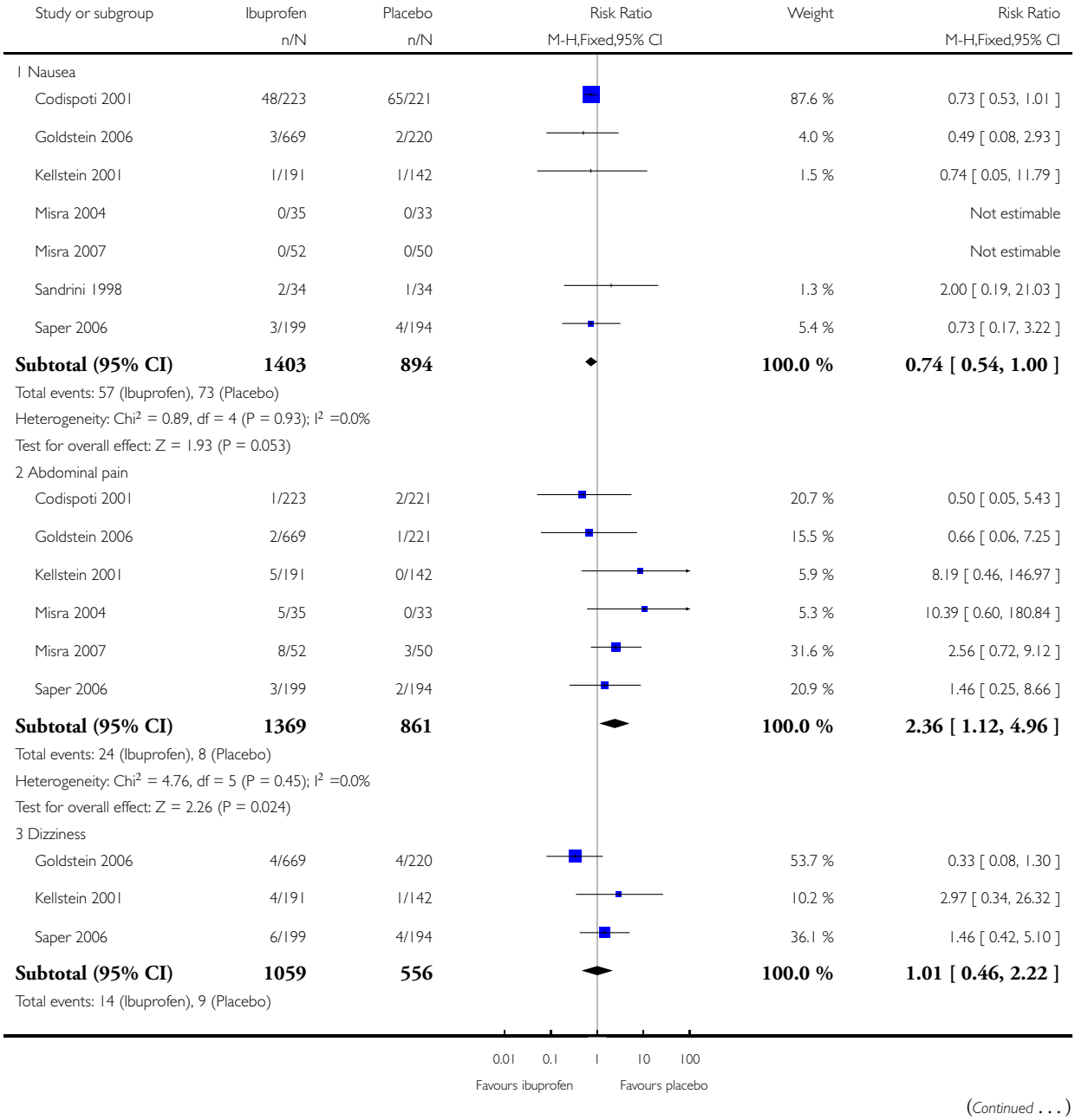
Test for subgroup differences: Not applicable

Analysis 2.6. Comparison 2 Ibuprofen 400 mg versus placebo, Outcome 6 Specific adverse events.

Review: Ibuprofen with or without an antiemetic for acute migraine headaches in adults

Comparison: 2 Ibuprofen 400 mg versus placebo

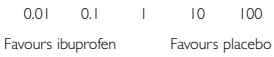
Outcome: 6 Specific adverse events



(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Ibuprofen n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Heterogeneity: Chi² = 3.83, df = 2 (P = 0.15); I² =48%					
Test for overall effect: Z = 0.02 (P = 0.98)					
4 Somnolence					
Goldstein 2006	5/669	1/220		36.7 %	1.64 [0.19, 14.00]
Kellstein 2001	3/191	0/142		14.0 %	5.21 [0.27, 100.14]
Misra 2007	0/52	0/50			Not estimable
Saper 2006	5/199	2/194		49.4 %	2.44 [0.48, 12.41]
Subtotal (95% CI)	**1111**	**606**		**100.0 %**	**2.53 [0.79, 8.17]**
Total events: 13 (Ibuprofen), 3 (Placebo)					
Heterogeneity: Chi² = 0.39, df = 2 (P = 0.82); I² =0.0%					
Test for overall effect: Z = 1.56 (P = 0.12)					



Analysis 2.7. Comparison 2 Ibuprofen 400 mg versus placebo, Outcome 7 Participants using rescue medication.

Review: Ibuprofen with or without an antiemetic for acute migraine headaches in adults

Comparison: 2 Ibuprofen 400 mg versus placebo

Outcome: 7 Participants using rescue medication

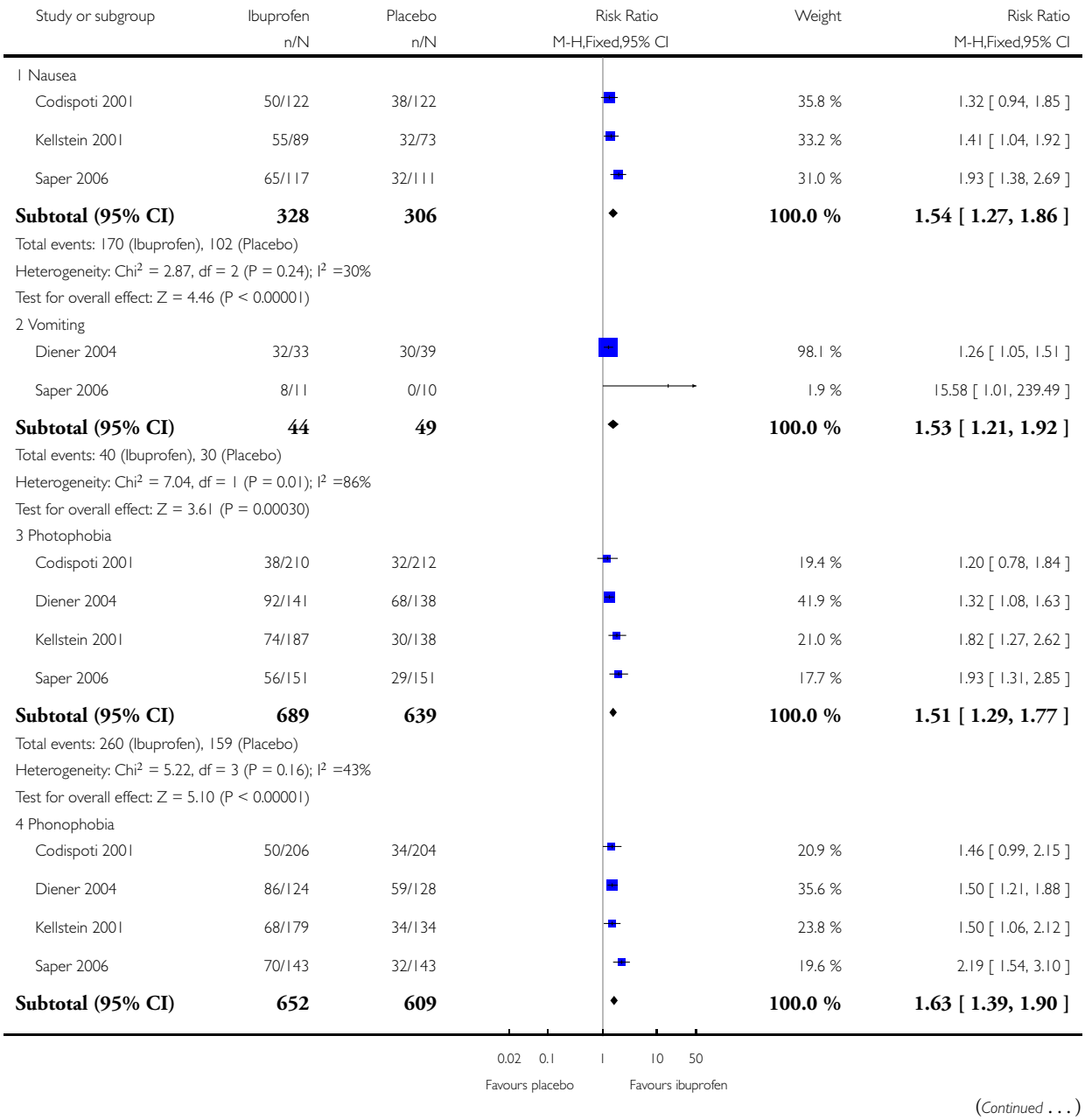
Study or subgroup	Ibuprofen n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Codispoti 2001	89/223	104/221		20.0 %	0.85 [0.69, 1.05]
Diener 2004	87/212	147/222		27.5 %	0.62 [0.51, 0.75]
Kellstein 2001	25/191	43/142		9.5 %	0.43 [0.28, 0.67]
Misra 2004	16/35	30/33		5.9 %	0.50 [0.34, 0.73]
Misra 2007	24/52	46/50		9.0 %	0.50 [0.37, 0.68]
Sandrini 1998	9/29	14/29		2.7 %	0.64 [0.33, 1.24]
Saper 2006	103/189	132/187		25.4 %	0.77 [0.66, 0.91]
Total (95% CI)	**931**	**884**		**100.0 %**	**0.67 [0.61, 0.74]**
Total events: 353 (Ibuprofen), 516 (Placebo)					
Heterogeneity: Chi^2 = 17.87, df = 6 (P = 0.01); I^2 =66%					
Test for overall effect: Z = 8.28 (P < 0.00001)					
Test for subgroup differences: Not applicable					

Analysis 2.8. Comparison 2 Ibuprofen 400 mg versus placebo, Outcome 8 Relief of associated symptoms at 2 h.

Review: Ibuprofen with or without an antiemetic for acute migraine headaches in adults

Comparison: 2 Ibuprofen 400 mg versus placebo

Outcome: 8 Relief of associated symptoms at 2 h



(*Continued . . .*)

(. . . *Continued*)

Study or subgroup	Ibuprofen n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Total events: 274 (Ibuprofen), 159 (Placebo)					
Heterogeneity: Chi^2 = 3.79, df = 3 (P = 0.29); I^2 =21%					
Test for overall effect: Z = 6.13 (P < 0.00001)					

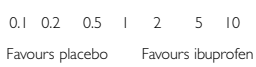
Analysis 2.9. Comparison 2 Ibuprofen 400 mg versus placebo, Outcome 9 Relief of functional disability at 2 hours.

Review: Ibuprofen with or without an antiemetic for acute migraine headaches in adults

Comparison: 2 Ibuprofen 400 mg versus placebo

Outcome: 9 Relief of functional disability at 2 hours

Study or subgroup	Ibuprofen n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Codispoti 2001	39/218	27/210		19.7 %	1.39 [0.88, 2.19]
Kellstein 2001 (1)	139/184	77/141		62.4 %	1.38 [1.17, 1.64]
Saper 2006	67/181	25/180		17.9 %	2.67 [1.77, 4.02]
Total (95% CI)	**583**	**531**		**100.0 %**	**1.61 [1.38, 1.89]**
Total events: 245 (Ibuprofen), 129 (Placebo)					
Heterogeneity: Chi^2 = 9.27, df = 2 (P = 0.01); I^2 =78%					
Test for overall effect: Z = 5.87 (P < 0.00001)					
Test for subgroup differences: Not applicable					



(1) Reduced to none or mild

Analysis 3.1. Comparison 3 Ibuprofen 400 mg versus rofecoxib 25 mg, Outcome 1 Headache relief at 2 hours.

Review: Ibuprofen with or without an antiemetic for acute migraine headaches in adults

Comparison: 3 Ibuprofen 400 mg versus rofecoxib 25 mg

Outcome: 1 Headache relief at 2 hours

Study or subgroup	ibuprofen n/N	rofecoxib n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Misra 2004	19/35	15/33		12.2 %	1.19 [0.74, 1.93]
Saper 2006	109/189	111/187		87.8 %	0.97 [0.82, 1.15]
Total (95% CI)	**224**	**220**		**100.0 %**	**1.00 [0.85, 1.17]**

Total events: 128 (ibuprofen), 126 (rofecoxib)

Heterogeneity: $Chi^2 = 0.63$, df = 1 (P = 0.43); $I^2 = 0.0\%$

Test for overall effect: Z = 0.02 (P = 0.99)

Test for subgroup differences: Not applicable

Analysis 3.2. Comparison 3 Ibuprofen 400 mg versus rofecoxib 25 mg, Outcome 2 Sustained headache relief over 24 hours.

Review: Ibuprofen with or without an antiemetic for acute migraine headaches in adults

Comparison: 3 Ibuprofen 400 mg versus rofecoxib 25 mg

Outcome: 2 Sustained headache relief over 24 hours

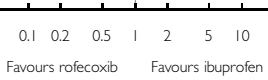
Study or subgroup	ibuprofen n/N	rofecoxib n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Misra 2004	15/35	12/33		14.4 %	1.18 [0.65, 2.13]
Saper 2006	59/189	73/187		85.6 %	0.80 [0.61, 1.06]
Total (95% CI)	**224**	**220**		**100.0 %**	**0.85 [0.66, 1.10]**

Total events: 74 (ibuprofen), 85 (rofecoxib)

Heterogeneity: $Chi^2 = 1.35$, df = 1 (P = 0.24); $I^2 = 26\%$

Test for overall effect: Z = 1.23 (P = 0.22)

Test for subgroup differences: Not applicable



Analysis 3.3. Comparison 3 Ibuprofen 400 mg versus rofecoxib 25 mg, Outcome 3 Participants using rescue medication.

Review: Ibuprofen with or without an antiemetic for acute migraine headaches in adults

Comparison: 3 Ibuprofen 400 mg versus rofecoxib 25 mg

Outcome: 3 Participants using rescue medication

Study or subgroup	ibuprofen n/N	rofecoxib n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Misra 2004	16/35	18/33		18.0 %	0.84 [0.52, 1.35]
Saper 2006	103/189	84/187		82.0 %	1.21 [0.99, 1.49]
Total (95% CI)	**224**	**220**		**100.0 %**	**1.15 [0.95, 1.38]**

Total events: 119 (ibuprofen), 102 (rofecoxib)

Heterogeneity: Chi^2 = 1.95, df = 1 (P = 0.16); I^2 =49%

Test for overall effect: Z = 1.42 (P = 0.16)

Test for subgroup differences: Not applicable

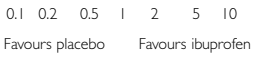
Analysis 4.1. Comparison 4 Ibuprofen 600 mg versus placebo, Outcome 1 Pain-free at 2 hours.

Review: Ibuprofen with or without an antiemetic for acute migraine headaches in adults

Comparison: 4 Ibuprofen 600 mg versus placebo

Outcome: 1 Pain-free at 2 hours

Study or subgroup	Ibuprofen n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kellstein 2001	58/198	19/142		100.0 %	2.19 [1.37, 3.51]
Total (95% CI)	**198**	**142**		**100.0 %**	**2.19 [1.37, 3.51]**
Total events: 58 (Ibuprofen), 19 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.26 (P = 0.0011)					
Test for subgroup differences: Not applicable					



Analysis 4.2. Comparison 4 Ibuprofen 600 mg versus placebo, Outcome 2 Headache relief at 2 hours.

Review: Ibuprofen with or without an antiemetic for acute migraine headaches in adults

Comparison: 4 Ibuprofen 600 mg versus placebo

Outcome: 2 Headache relief at 2 hours

Study or subgroup	Ibuprofen n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kellstein 2001	142/198	71/142		100.0 %	1.43 [1.19, 1.73]
Total (95% CI)	**198**	**142**		**100.0 %**	**1.43 [1.19, 1.73]**
Total events: 142 (Ibuprofen), 71 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.80 (P = 0.00015)					
Test for subgroup differences: Not applicable					

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 two hours - number of participants with a pain intensity of 0 (none) at two hours after administration of study medication, expressed as a fraction of the treated participants with the appropriate baseline pain.

• Headache relief at two hours - number of participants with a reduction in pain intensity from 2/3 (moderate/severe) to 0/1 (none/mild) at two 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 two 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 two 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 two 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 two 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. Ibuprofen/
2. (ibuprofen OR brufen OR propionic acid OR isobutylphenyl propionic acid).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. Ibuprofen/
2. (ibuprofen OR brufen OR propionic acid OR isobutylphenyl propionic acid).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. 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 Cochrane CENTRAL

1. MeSH descriptor Ibuprofen
2. (ibuprofen OR brufen OR propionic acid OR isobutylphenyl propionic acid):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 efficacy outcomes: headache relief, pain-free, and use of rescue medication

Study ID	Treatment	HR 1 h	HR 2 h	PF 2 h	24 h SHR	24 h SPF	Use of rescue medication
Codispoti 2001	(1) Ibuprofen 200 mg, n = 216 (2) Ibuprofen 400 mg, n = 223 (3) Placebo, n	(1) 60/216 (2) 56/223 (3) 46/221	(1) 90/216 (2) 91/223 (3) 62/221	(1) 34/216 (2) 31/223 (3) 17/221	No usable data	No usable data	(1) 79/216 (2) 89/223 (3) 104/221

(*Continued*)

	= 221						
Diener 2004	(1) Ibuprofen 400 mg, n = 212 (2) Aspirin 1000 mg, n = 222 (3) Sumatriptan 50 mg, n = 226 (4) Placebo, n = 222	(1) 66/212 (2) 76/222 (3) 54/226 (4) 25/222	(1) 128/212 (2) 116/222 (3) 125/226 (4) 68/222	(1) 70/212 (2) 60/222 (3) 83/226 (4) 28/222	No usable data	No usable data	(1) 87/212 (2) 100/222 (3) 92/224 (4) 147/222
Ellis 1993	(1) Ibuprofen 600 mg + IV placebo, n = 10 (2) Placebo tablet + IV placebo, n = 10 (3) Ibuprofen 600 mg + metoclopramide 1 mg, n = 10 (4) Placebo tablet + IV metoclopramide 1 mg, n = 10	No data	No data	No data	No data	No data	(1) 7/10 (2) 8/10 (3) 4/110 (4) 1/10
Goldstein 2006	(1) Ibuprofen 400 mg, n = 669 (2) Paracetamol/aspirin/caffeine 500/500/130 mg, n = 669 (3) Placebo, n = 221	No data	No data	(1) 186/669 (3) 53/220	No data	No data	No usable data
Kellstein 2001	(1) Ibuprofen liquigel 200 mg, n = 198 (2) Ibuprofen liquigel 400 mg, n = 191	(1) 81/198 (2) 92/191 (3) 107/198 (4) 37/142	(1) 127/198 (2) 138/191 (3) 142/198 (4) 71/142	(1) 50/198 (2) 53/191 (3) 58/198 (4) 19/142	(1) 106/198 (2) 111/191 (3) 121/198 (4) 50/142	No data	(1) 33/198 (2) 25/191 (3) 27/198 (4) 43/142

(*Continued*)

	(3) Ibuprofen liquigel 600 mg, n = 198 (4) Placebo, n = 142						
Misra 2004	(1) Ibuprofen 400 mg, n = 40 (2) Rofecoxib 25 mg, n = 42 (3) Placebo, n = 42	No data	(1) 19/35 (2) 15/33 (3) 3/33	No data	(1) 15/35 (2) 12/33 (3) 2/33	No data	(1) 16/35 (2) 18/33 (3) 30/33
Misra 2007	(1) Ibuprofen 400 mg, n = 55 (2) Rizatriptan 10 mg, n = 57 (3) Placebo, n = 53	No data	(1) 28/52 (2) 39/53 (3) 4/50	(1) 16/52 (2) 20/53 (3) 1/50	(1) 23/52 (2) 33/53 (3) 3/50	No data	(1) 24/52 (2) 14/53 (3) 46/50
Sandrini 1998	(1) Ibuprofen arginine 400 mg, n = 34 (2) Placebo, n = 34	(1) 12/29 (2) 0/29	(1) 15/29 (2) 2/29	No data	No data	No data	(1) 9/29 (2) 14/29
Saper 2006	Ibuprofen 400 mg, n = 199 Rofecoxib 25 mg, n = 194 Rofecoxib 50 mg, n = 196 Placebo, n = 194	No data	(1) 109/189 (2) 111/187 (3) 117/188 (4) 57/187	(1) 45/189 (2) 49/187 (3) 50/188 (4) 10/187	(1) 59/189 (2) 73/187 (3) 75/188 (4) 25/187	(1) 34/189 (2) 38/187 (3) 34/188 (4) 5/187	(1) 103/189 (2) 84/187 (3) 90/188 (4) 132/187

Appendix 6. Summary of outcomes: adverse events and withdrawals

Study ID	Treatment	Any AE	Specific AEs	Serious AEs	AE withdrawal	Other withdrawals/ exclusions
Codispoti 2001	(1) Ibuprofen 200 mg, n = 216	(1) 71/216 (2) 77/223	Commonly reported "drug-re-	None	(1) 0/216 (2) 2/223	None

(*Continued*)

	(2) Ibuprofen 400 mg, n = 223 (3) Placebo, n = 221	(3) 82/221	lated AEs": Abdominal pain (1) 3, (2) 1, (3) 2 Nausea (1) 53, (2) 48, (3) 65 Vomiting (1) 9, (2) 10, (3) 20		(3) 3/221 All nausea or vomiting	
Diener 2004	(1) Ibuprofen 400 mg, n = 212 (2) Aspirin 1000 mg, n = 222 (3) Sumatriptan 50 mg, n = 226 (4) Placebo, n = 222	(1) 27/212 (2) 36/222 (3) 45/226 (4) 32/222	No data	(1) 1/212 (perforation of a duodenal ulcer) (2) 1/222 (renal colic) (3) 0/226 (4) 0/222	Possibly 2 serious AEs, but unconfirmed	I treated participant excluded from analyses - did not return diary card
Ellis 1993	(1) Ibuprofen 600 mg + IV placebo, n = 10 (2) Placebo tablet + IV placebo, n = 10 (3) Ibuprofen 600 mg + metoclopramide 1 mg, n = 10 (4) Placebo tablet + IV metoclopramide 1 mg, n = 10	No data	No data	No data	No data	None
Goldstein 2006	(1) Ibuprofen 400 mg, n = 669 (2) Paracetamol/aspirin/caffeine 500/500/130 mg, n = 669 (3) Placebo, n = 221	(1) 34/669 (2) 65/666 (3) 12/220	Dyspepsia (1) 2, (3) 1 Nausea (1) 3, (3) 2 Vomiting (1) 2, (3) 1 Dizziness (1) 4, (3) 4 Somnolence (1) 5, (3) 1	None	None	No post-baseline data: (2) 3, (3) 1
Kellstein 2001	(1) Ibuprofen liquigel 200 mg, n = 198 (2) Ibuprofen	(1) 19/200 (2) 26/193 (3) 32/199 (4) 19/143	Severe drug-related AEs: Dyspepsia (1) 2, (2) 5, (3) 2, (4) 0	None	None	None

(*Continued*)

	liquigel 400 mg, n = 191 (3) Ibuprofen liquigel 600 mg, n = 198 (4) Placebo, n = 142		Dizziness (1) 3, (2) 4, (3) 2, (4) 1 Somnolence (1) 2, (2) 3, (3) 5, (4) 0 Nausea (1) 2, (2) 1, (3) 1, (4) 1 Nervousness (3) 1 Tremor (4) 1			
Misra 2004	(1) Ibuprofen 400 mg, n = 40 (2) Rofecoxib 25 mg, n = 42 (3) Placebo, n = 42	(1) 5/35 2) 0/33 (3) Not reported	Abdominal pain (1) 5 (one severe)	None	(1) ?1/35 (2) 0/33 (3) 0/33	Lost to follow-up: (1) 6/40, (2) 9/42, (3) 8/42
Misra 2007	(1) Ibuprofen 400 mg, n = 55 (2) Rizatriptan 10 mg, n = 57 (3) Placebo, n = 53	(1) 8/52 (2) 9/53 (3) 3/50 All mild to moderate	Gastric discomfort (1) 8, (2) 1, (3) 3 Palpitation (2) 6 Somnolence (2) 2	None	None	Lost to follow-up: (1) 3/55, (2) 4/57, (3) 3/53
Sandrini 1998	(1) Ibuprofen arginine 400 mg, n = 34 (2) Placebo, n = 34	(1) 3/34 (2) 4/34 All slight and transient	Nausea (1) 2, (2) 1 Drowsiness (1) 1 Pyrosis (2) 2 Oedema (2) 1	None	None	None
Saper 2006	Ibuprofen 400 mg, n = 199 Rofecoxib 25 mg, n = 194 Rofecoxib 50 mg, n = 196 Placebo, n = 194	(1) 56/199 (2) 62/194 (3) 74/196 (4) 54/194	Drug-related: Dry mouth (1) 9, (2) 9, (3) 6, (4) 7 Dyspepsia (1) 3, (2) 4, (3) 2, (4) 2 Nausea (1) 3, (2) 3, (3) 8, (4) 4 Dizziness (1) 6, (2) 9, (3) 9, (4) 4 Somnolence (1) 5, (2) 4, (3) 7, (4) 2	No serious drug-related AEs	(1) 1/199 (death from sepsis)	Excluded from efficacy analysis (no reason given): (1) 10, (2) 7, (3) 8, (4) 7

Appendix 7. Other outcomes

Use of rescue medication

Most studies asked participants whose symptoms were not adequately controlled to wait for two hours before taking any additional medication in order to give the test medication enough time to have an effect; Ellis 1993 asked participants to wait at least one hour. 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).

Ibuprofen 200 mg versus placebo

Two studies (777 participants) reported on use of rescue medication (Codispoti 2001; Kellstein 2001).

- The proportion of participants using rescue medication after ibuprofen 200 mg was 27% (112/414; range 17% to 37%).
- The proportion of participants using rescue medication after placebo was 40% (147/363; range 30% to 47%).
- The relative benefit of treatment compared to placebo was 0.70 (0.58 to 0.86); the NNT to prevent use of rescue medication was 7.4 (5.0 to 15) (Analysis 1.5).

Ibuprofen 400 mg versus placebo

Seven studies (1815 attacks) reported on use of rescue medication (Codispoti 2001; Diener 2004; Kellstein 2001; Misra 2004; Misra 2007; Sandrini 1998; Saper 2006).

- The proportion of attacks using rescue medication after ibuprofen 400 mg was 38% (353/931; range 13% to 54%).
- The proportion of attacks using rescue medication after placebo was 58% (516/884; range 30% to 92%).
- The relative benefit of treatment compared to placebo was 0.67 (0.61 to 0.74); the NNT to prevent use of rescue medication was 4.9 (4.0 to 6.2) (Analysis 2.7).

Ibuprofen 400 mg versus rofecoxib 25 mg

Two studies (444 participants) provided data for a direct comparison of ibuprofen 400 mg and rofecoxib 25 mg for use of rescue medication (Misra 2004; Saper 2006).

- The proportion of participants using rescue medication with ibuprofen 400 mg was 53% (119/224; range 46% to 54%).
- The proportion of participants using rescue medication with rofecoxib 25 mg was 46% (102/220; range 45% to 55%).
- The relative benefit of ibuprofen compared to rofecoxib was 1.2 (0.95 to 1.4); the NNT was not calculated (Analysis 3.3).

Relief of migraine-associated symptoms

Relief of migraine-associated symptoms (nausea, vomiting, photophobia, phonophobia) was not consistently reported. Four studies (Codispoti 2001; Diener 2004; Kellstein 2001; Saper 2006) reported baseline incidence and dichotomous data for symptom relief two hours after taking study medication.

Effects of treatment on relieving associated symptoms in these studies with dichotomous data are presented in the table below. Ibuprofen significantly relieved all four symptoms after two hours compared with placebo, with a trend for lower (better) NNTs with 400 mg (Analysis 2.8) than with 200 mg (Analysis 1.6) for nausea, photophobia and phonophobia. NNTs for relief of these three symptoms ranged from 7 to 13 with ibuprofen 200 mg and from 5 to 8 with ibuprofen 400 mg.

Goldstein 2006 did not report dichotomous data, but did report that the proportion of participants free of migraine-associated symptoms was significantly higher for ibuprofen 400 mg than for placebo at most time points. Misra 2004 reported that the proportion of participants with relief of associated symptoms at two hours was significantly higher with ibuprofen 400 mg (50%) and rofecoxib 25 mg (39%) than with placebo (9%), and Misra 2007 reported significant mean improvement in associated symptoms with ibuprofen 400 mg compared to placebo at two hours.

Summary of results: relief of associated symptoms two hours after taking study medication						
Intervention	**Studies**	**Attacks with symptom present**	**Treatment (%)**	**Placebo (%)**	**RR (95% CI)**	**NNT (95% CI)**
Nausea						
Ibuprofen 200 mg versus placebo	2	429	49	36	1.3 (1.1 to 1.7)	7.6 (4.4 to 25)
Ibuprofen 400 mg versus placebo	3	634	52	33	1.5 (1.3 to 1.9)	5.4 (3.8 to 9.1)
Vomiting						
Ibuprofen 400 mg versus placebo	2	270	91	61	1.5 (1.2 to 1.9)	3.4 (2.2 to 7.1)
Photophobia						
Ibuprofen 200 mg versus placebo	2	751	25	18	1.4 (1.1 to 1.9)	13 (7.4 to 53)
Ibuprofen 400 mg versus placebo	4	1328	38	25	1.5 (1.3 to 1.8)	7.8 (5.6 to 13)
Phonophobia						
Ibuprofen 200 mg versus placebo	2	724	29	20	1.4 (1.1 to 1.8)	11 (6.5 to 34)
Ibuprofen 400 mg versus placebo	4	1261	42	26	1.6 (1.4 to 1.9)	6.3 (4.8 to 9.3)

The analysis for vomiting has to be interpreted with caution due to the small number of participants (< 100) experiencing vomiting at baseline. In the placebo arm of Saper 2006 four *more* participants had vomiting at two hours than at baseline.
There were insufficient data comparing ibuprofen with active comparators for analysis of associated symptoms.

Functional disability

Only three studies (Codispoti 2001; Kellstein 2001; Saper 2006) reported baseline incidence and dichotomous data for relief of functional disability associated with migraine headaches. All three studies used a four-point scale to measure severity of functional

disability, but used slightly different wording; nearly all (>95%) participants had some degree of functional disability at baseline, and in 25% to 30% this was scored as mild. Two studies reported the numbers of participants with no residual disability at two hours, but Kellstein reported the number with no or mild disability at two hours, and consequently has higher event rates, but the studies were combined for analysis.

Ibuprofen 200 mg versus placebo

- The proportion of participants with relief of functional disability at two hours after ibuprofen 200 mg was 46% (187/406; range 21% to 73%).
- The proportion of participants with relief of functional disability at two hours after placebo was 30% (104/351; range 13% to 55%).
- The relative benefit of treatment compared to placebo was 1.4 (1.2 to 1.7); the NNT to relieve functional disability was 6.1 (4.3 to 10) Analysis 1.7).

Ibuprofen 400 mg versus placebo

- The proportion of participants with relief of functional disability at two hours after ibuprofen 400 mg was 42% (245/583; range 18% to 76%).
- The proportion of participants with relief of functional disability at two hours after placebo was 24% (129/531; range 13% to 55%).
- The relative benefit of treatment compared to placebo was 1.6 (1.4 to 1.9); the NNT to relieve functional disability was 5.6 (4.3 to 8.1) Analysis 2.6).

There was no obvious benefit of 400 mg over 200 mg. Overall significantly more participants treated with ibuprofen 200 mg and 400 mg than with placebo experienced relief of functional disability at two hours. Functional disability rated as severe or requiring bed rest was significantly reduced with ibuprofen compared with placebo, with a trend for lower (better) NNTps with the higher dose. In the placebo arm of Saper 2006 three *more* participants had severe functional disability with placebo at two hours than at baseline.
Goldstein 2006 reported that the proportion of participants without any functional disability was significantly higher for ibuprofen 400 mg than for placebo, and Misra 2007 reported significant mean improvement in functional disability with ibuprofen 400 mg compared to placebo at two hours.

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 10, 2010

Date	Event	Description
6 September 2017	Review declared as stable	See Published notes.
3 October 2016	Amended	Minor reporting error fixed in Effects of interventions.
7 May 2013	Review declared as stable	This review will be assessed for further updating in 2018.
14 February 2013	New citation required but conclusions have not changed	No new studies identified.
14 February 2013	New search has been performed	New searches carried out, Risk of bias tables expanded and updated, Summary of findings table added

CONTRIBUTIONS OF AUTHORS

All authors were involved with planning and writing the protocol. For the full review, RR and SD carried out searches, selected studies for inclusion and performed data extraction and analysis. RAM was involved with analysis. HJM acted as arbitrator. All authors were involved with writing.

For the update, SD carried out searches. RAM and SD updated the review. All authors read and approved the update.

DECLARATIONS OF INTEREST

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. RR has no such interests to declare. The Oxford Pain Research Trust, the NHS Cochrane Collaboration Programme Grant Scheme, and the NIHR Biomedical Research Centre Programme provided support for the original review. The Oxford Pain Research Trust provided support for the update. None had any input into the review at any stage.

SOURCES OF SUPPORT

Internal sources

- Oxford Pain Research Trust, UK.

General institutional support

External sources

- *Lifting The Burden:* the Global Campaign against Headache, UK.

Funding for administrative costs associated with editorial and peer review

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For the original review we included an outcome that was not specified in the protocol. 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 indicating 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.

The protocol stated that "Studies reporting treatment of consecutive headache episodes will be accepted if outcomes for the first, or each, episode were reported separately". Two studies (Misra 2004; Misra 2007) treated two or more attacks with single doses of the same study medication and reported results as numbers of participants with various responses. It is not clear how the data for multiple attacks were combined. We have included the data from these studies on the assumption that an individual's response was consistent across attacks, given that a sensitivity analysis was to be done excluding these studies on the grounds of potentially unreliable blinding.

For the update, 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 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)

Administration, Oral; Analgesics, Non-Narcotic [*therapeutic use]; Antiemetics [*therapeutic use]; Drug Therapy, Combination [methods]; Ibuprofen [*therapeutic use]; Migraine Disorders [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans