Published in final edited form as:
Cochrane Database Syst Rev. ; (10): CD008039. doi:10.1002/14651858.CD008039.pub2.

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

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Abstract

Background—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 Cochrane CENTRAL, MEDLINE, EMBASE and the Oxford Pain Relief Database for studies through 22 April 2010.

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—Nine 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,

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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.
Editorial group: Cochrane Pain, Palliative and Supportive Care Group.
Publication status and date: New, published in Issue 10, 2010.
Review content assessed as up-to-date: 21 April 2010.

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

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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 for 2-hour headache relief than the lower dose. Soluble formulations of ibuprofen 400 mg were better than standard tablets for 1-hour, but not 2-hour headache relief.

Associated symptoms of nausea, vomiting, photophobia and phonophobia and functional disability were reduced within 2 hours, and fewer participants used rescue medication with ibuprofen compared with placebo. Similar numbers of participants experienced adverse events, which were mostly mild and transient.

Ibuprofen 400 mg did not differ from rofecoxib 25 mg for 2-hour headache relief, 24-hour headache relief or use of rescue medication.

Authors' conclusions—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.

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

BACKGROUND

Description of the condition

Migraine is a common, disabling headache disorder, affecting about 12% of Western populations, and with considerable social and economic impact. It is more prevalent in women than men (on the order of 18% versus 6% 1-year prevalence), and in the age range 30 to 50 years (Hazard 2009; Lipton 2007; Moens 2007). The International Headache Society (IHS) classifies two major subtypes (IHS 2004). Migraine without aura is the most common, and usually more disabling, 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.

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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, disability, social functioning, quality of relationships, emotional well-being and general health (Edmeads 1993; Osterhaus 1994; Solomon 1997) results in a huge burden for the individual, health services and society (Clarke 1996; Ferrari 1998; Hazard 2009; Hu 1999; Solomon 1997). The annual US economic burden relating to migraine, including missed days of work and lost productivity, is US$14 billion (Hu 1999). Thus 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 increases economic productivity (Jhingran 1996; Lofland 1999).

Description of the intervention

Ibuprofen is an effective and well-tolerated NSAID which has been available as an OTC medication in the 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. 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 improve outcomes by alleviating the often incapacitating symptoms of nausea and vomiting, and (at least potentially) by enhancing the bioavailability of the co-administered analgesic. In particular, prokinetic antiemetics such as metoclopramide, which stimulate gastric emptying, may improve outcomes by increasing absorption of the analgesic. 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.

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.

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—Randomised, double-blind, placebo- or active-controlled studies using ibuprofen to treat a migraine headache episode were included. 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. Studies reporting treatment of consecutive headache episodes were accepted if outcomes for the first, or each, episode were reported separately. Cross-over studies were accepted if there was adequate washout (≥ 48 hours) between treatments.

Types of participants—Studies included adults (at least 18 years of age) with migraine. The diagnosis of migraine specified by the International Headache Society (IHS 1988; IHS 2004) was used, although other definitions were considered if they conformed in general to IHS diagnostic criteria. There were no restrictions on migraine frequency, duration or type (with or without aura). Participants taking stable prophylactic therapy to reduce migraine frequency were accepted; details on any prophylactic therapy prescribed or allowed are provided in the Characteristics of included studies table.

Types of interventions—Included studies had to use either a single dose of ibuprofen to treat a migraine headache episode when pain was of moderate to severe intensity, or investigate different dosing strategies and/or timing 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 be self-administered. A placebo comparator is essential to demonstrate that ibuprofen is effective in this condition. Active-controlled trials without a placebo would be considered as secondary evidence. Studies to demonstrate prophylactic efficacy in reducing the number or frequency of migraine headaches were not included.

Types of outcome measures

Primary outcomes: The choice of main outcome measures for this review was made by taking into consideration scientific rigour, availability of data and patient preferences (Lipton 1999). Patients with acute migraine headaches have rated complete pain relief, no headache recurrence, rapid onset of pain relief, and no side effects as the four most important outcomes (Lipton 1999).

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

- Pain-free at 2 hours, without the use of rescue medication;
- Reduction in headache pain (’headache relief’) at 1 and 2 hours (pain reduced from moderate or severe to none or mild without the use of rescue medication);
- Sustained pain-free over 24 hours (pain-free within 2 hours, with no use of rescue medication or recurrence within 24 hours);
- Sustained pain reduction over 24 hours (headache relief at 2 hours, sustained for 24 hours, with no use of rescue medication or a second dose of study medication).

Pain intensity or pain relief were measured by the patient (not the investigator or carer). Pain measures accepted for the primary outcomes were:

- Pain intensity (PI): 4-point categorical scale, with wording equivalent to none, mild, moderate and severe; or 100 mm VAS;

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

Only data obtained directly from the patient were considered.

Secondary outcomes: Secondary outcomes considered included:

- Participants with any adverse event over 24 hours post dose;
- Participants with particular adverse events over 24 hours post dose;
- Withdrawals due to adverse events over 24 hours post dose;
- Relief of headache-associated symptoms;
- Functional disability.

Search methods for identification of studies

Electronic searches—The following electronic databases were searched:

- Cochrane CENTRAL, latest search 22 April 2010;
- MEDLINE (via Ovid) latest search 22 April 2010;
- EMBASE (via Ovid) latest search 22 April 2010;
- Oxford Pain Relief Database (Jadad 1996a).

See Appendix 1 for the search strategy for MEDLINE (via OVID), Appendix 2 for the search strategy for EMBASE, and Appendix 3 for the search strategy for CENTRAL. There were no language restrictions.

Searching other resources—Reference lists of retrieved studies and review articles were searched for additional studies. 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. Titles and abstracts of all studies identified by electronic searches were viewed on screen, and any that clearly did not satisfy inclusion criteria were excluded. Full copies of the remaining studies were read 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 from. Disagreements were settled by discussion with a third review author. Data was entered into RevMan 5.0 by one author.

Assessment of risk of bias in included studies—Methodological quality was assessed using the Oxford Quality Score (Jadad 1996b).

The scale is used as follows.

- Is the study randomised? If yes, give one point.

- Is the randomisation procedure reported and is it appropriate? If yes, add one point; if no, deduct one point.
- Is the study double blind? If yes, add one point.
- Is the double blind method reported and is it appropriate? If yes, add one point; if no, deduct one point.
- Are the reasons for patient withdrawals and dropouts described? If yes, add one point.

The scores for each study are reported in the Characteristics of included studies table.

A risk of bias table was also completed, using assessments of randomisation, allocation concealment and blinding.

Measures of treatment effect—Relative risk (or 'risk ratio', RR) were used to establish statistical difference. Numbers needed to treat (NNT) and pooled percentages were used 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 occur 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 occur 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—We accepted randomisation to individual patient only.

Dealing with missing data—The most likely source of missing data is in cross-over studies. Where this was an issue only first-period data were used.

Assessment of heterogeneity—Heterogeneity of studies was assessed visually (L'Abbe 1987).

Data synthesis—Studies using a single dose of ibuprofen in established pain of at least moderate intensity were analysed separately from studies in which medication was taken before pain was well established or in which a second dose of medication is permitted.

Effect sizes were calculated and data combined for analysis only for comparisons and outcomes where there were at least two studies and 200 participants (Moore 1998). In case only one study on relevant outcomes in at least 200 participants was available, prohibiting combining of data for analysis, a summary of data on relevant outcomes is provided. Relative risk of benefit or harm was calculated with 95% confidence intervals (CIs) using a fixed-effect model (Morris 1995). NNT, NNTp and NNH with 95% CIs were calculated using the pooled number of events by the method of Cook and Sackett (Cook 1995). A

statistically significant difference from control was assumed when the 95% CI of the relative risk of benefit or harm included the number one.

Significant differences between NNT, NNTp and NNH for different groups in subgroup and sensitivity analyses, were determined using the z test (Tramer 1997).

Subgroup analysis and investigation of heterogeneity—Issues for subgroup analysis are dose, monotherapy or combination with an antiemetic, formulation, and route of administration. For combined treatment with an antiemetic, different antiemetics would be compared if there were sufficient data.

Sensitivity analysis—Sensitivity analysis was anticipated 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

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search—Thirteen studies were identified as potentially suitable for the review. We are aware that two unpublished studies may have been performed by a pharmaceutical company some years ago, but we were unable to obtain any useful information and have no direct knowledge that they actually exist; trial reports could not be retrieved at the time of writing, but they will be included in an update if they become available.

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.

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 1 and 2 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 and blinding. None of the included studies was at high risk of bias (Figure 1).

Effects of interventions

Details of outcomes in individual studies are provided in Appendix 4 (efficacy) Appendix 5 (migraine-associated symptoms) and Appendix 6 (adverse events and withdrawals).

Pain-free at 2 hours

Ibuprofen 200 mg versus placebo: Two studies provided data for pain-free response at 2 hours (777 participants). One study used a standard oral formulation (Codispoti 2001) and the other a liquigel formulation (Kellstein 2001) (Analysis 1.1).

- The proportion of participants pain-free at 2 hours with ibuprofen 200 mg was 20% (84/414; range 16% to 25%).
- The proportion of participants pain-free at 2 hours with placebo was 10% (36/363; range 8% to 13%).
- The relative benefit of treatment compared to placebo was 2.0 (1.4 to 2.8).
- The NNT for pain-free response at 2 hours was 9.7 (6.5 to 18).

Ibuprofen 400 mg versus placebo

Standard and soluble formulations combined: Six studies provided data for pain-free response at 2 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) (Figure 2).

- The proportion of participants pain-free at 2 hours with ibuprofen 400 mg was 26% (401/1553; range 14% to 33%)

- The proportion of participants pain-free at 2 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 for pain-free response at 2 hours was 7.2 (5.9 to 9.2).

Subgroup analysis for formulation: For the five studies using standard formulations (2242 participants) 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 2 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).

Headache relief at 1 hour

Ibuprofen 200 mg versus placebo: Two studies provided data for headache relief at 1 hour (777 participants). One study used a standard oral formulation (Codispoti 2001) and the other a liquigel formulation (Kellstein 2001) (Analysis 1.2).

- The proportion of participants experiencing headache relief at 1 hour with ibuprofen 200 mg was 34% (141/414; range 8% to 41%).
- The proportion of participants experiencing headache relief at 1 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 for headache relief at 1 hour was 8.9 (5.7 to 20).

Ibuprofen 400 mg versus placebo

Standard and soluble formulations combined: Four studies provided data for headache relief at 1 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) (Analysis 2.2).

- The proportion of participants experiencing headache relief at 1 hour with ibuprofen 400 mg was 35% (226/655; range 25% to 48%).
- The proportion of participants experiencing headache relief at 1 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 for headache relief at 1 hour was 5.9 (4.6 to 8.2).

Subgroup analysis for formulation: The two studies using soluble preparations (391 participants) gave an NNT of 3.9 (2.9 to 6.0), while the two studies using standard preparations (878 participants) 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 1 hour.

Ibuprofen 600 mg versus placebo: Only one study (Kellstein 2001) provided data for headache relief at 1 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 4).

Headache relief at 2 hours

Ibuprofen 200 mg versus placebo: Two studies provided data for headache relief at 2 hours (777 participants). One study used a standard oral formulation (Codispoti 2001) and the other a liquigel formulation (Kellstein 2001) (Analysis 1.3).

- The proportion of participants experiencing headache relief at 2 hour with ibuprofen 200 mg was 52% (217/414; range 42% to 64%).
- The proportion of participants experiencing headache relief at 2 hour 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 for headache relief at 2 hours was 6.3 (4.4 to 11).

Ibuprofen 400 mg versus placebo

Standard and soluble formulations combined: Seven studies provided data for headache relief at 2 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) (Figure 5).

- The proportion of participants experiencing headache relief at 2 hours with ibuprofen 400 mg was 57% (528/931; range 41% to 72%).
- The proportion of participants experiencing headache relief at 2 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 for headache relief at 2 hours was 3.2 (2.8 to 3.7).

Subgroup analysis for formulation: The two studies using soluble preparations (391 participants) gave an NNT of 3.7 (2.7 to 5.8), while the two studies using standard preparations (1428 participants) 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 2 hours.

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

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 2 hours gave z = 3.761, P = 0.0002. Ibuprofen 400 mg was significantly better than ibuprofen 200 mg for headache relief at 2 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 2 hours (444 participants, Misra 2004; Saper 2006) (Analysis 3.1).

- The proportion of participants experiencing headache relief at 2 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).
- There was no difference between treatments.

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

Standard and soluble formulations combined: 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) (Analysis 2.4).

- 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 for sustained headache relief at 24 hours was 4.0 (3.2 to 5.2).

Subgroup analysis for formulation: The three studies using standard preparations (546 participants) gave an NNT of 4.2 (3.3 to 5.8).

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) (Analysis 3.2).

- 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.

Summary of results A: Pain-free and headache relief

	Studies	Participants	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)	
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 2 hours: Removing Misra 2007 from the analysis of ibuprofen 400 mg versus placebo gave a relative benefit of 1.8 (1.5 to 2.2) and NNT of 7.6 (6.2 to 9.9).

Headache relief at 2 hours: Removing Misra 2004 and Misra 2007 from the analysis of ibuprofen 400 mg versus placebo gave a relative benefit of 2.0 (1.8 to 2.3) and NNT of 3.3 (2.9 to 3.9).

Sustained headache relief at 24 hours: Removing Misra 2004 and Misra 2007 from the analysis of ibuprofen 400 mg versus placebo gave a relative benefit of 1.9 (1.5 to 2.3) and NNT of 4.6 (3.5 to 6.6).

Use of rescue medication

Ibuprofen 200 mg versus placebo: Two studies (777 participants) reported on use of rescue medication (Codispoti 2001; Kellstein 2001) (Analysis 1.4).

- 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).

Ibuprofen 400 mg versus placebo: Seven studies (1815 participants) reported on use of rescue medication (Codispoti 2001; Diener 2004; Kellstein 2001; Misra 2004; Misra 2007; Sandrini 1998; Saper 2006) (Analysis 2.5).

- The proportion of participants using rescue medication after ibuprofen 400 mg was 38% (353/931; range 13% to 54%).
- The proportion of participants 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).

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) (Analysis 3.3).

- 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.

Relief of migraine-associated symptoms: The 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 2 hours after taking study medication.

Effects of treatment on relieving associated symptoms in these studies with dichotomous data are presented in Summary of results B. Ibuprofen significantly relieved all four symptoms after 2 hours compared with placebo, with a trend for lower (better) NNTs with 400 mg (Analysis 2.7) 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. Fewer than 100 participants had vomiting at baseline, so this analysis should be interpreted with caution.

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 placebo at most time points. Misra 2004 reported that the proportion of participants with relief of associated symptoms at 2 hours was significantly higher with ibuprofen 400 mg (50%) and rofecoxib 25 mg (39%) than placebo (9%), and Misra 2007 reported significant mean improvement in associated symptoms with ibuprofen 400 mg compared to placebo at 2 hours.

Summary of results B: Relief of associated symptoms 2 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						

Intervention	Studies	Attacks with symptom present	Treatment (%)	Placebo (%)	RR (95% CI)	NNT (95% CI)
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)

Data from these studies were also analysed according to the presence of associated symptoms 2 hours after treatment, and NNTps calculated (Appendix 7). Significantly fewer participants experienced nausea, vomiting, photophobia or phonophobia 2 hours after taking study medication with ibuprofen than with placebo. Again, there was a trend for lower (better) NNTps with 400 mg (Analysis 2.8) than with 200 mg (Analysis 1.7) for nausea, photophobia and phonophobia. NNTps for presence of these three symptoms ranged from 12 to 18 with ibuprofen 200 mg and from 8 to 10 with ibuprofen 400 mg.

The analysis for vomiting has to be interpreted with caution due to the small number of participants experiencing vomiting at baseline. In the placebo arm of Saper 2006 four *more* participants had vomiting at 2 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 2 hours, but Kellstein reported the number with no or mild disability at 2 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 2 hours after ibuprofen 200 mg was 46% (187/406; range 21% to 73%).
- The proportion of participants with relief of functional disability at 2 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; Analysis 1.8).
- The NNT to relieve functional disability was 6.1 (4.3 to 10).

Ibuprofen 400 mg versus placebo

- The proportion of participants with relief of functional disability at 2 hours after ibuprofen 400 mg was 42% (245/583; range 18% to 76%).
- The proportion of participants with relief of functional disability at 2 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; Analysis 2.10).
- The NNT to relieve functional disability was 5.6 (4.3 to 8.1).

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 2 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 2 hours than at baseline.

Goldstein 2006 reported that the proportion of participants without any functional disability was significantly higher for ibuprofen 400 mg than placebo, and Misra 2007 reported significant mean improvement in functional disability with ibuprofen 400 mg compared to placebo at 2 hours.

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) (Analysis 1.5).

- 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.

Ibuprofen 400 mg versus placebo: Seven studies (1767 participants) 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) (Analysis 2.6).

- 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.

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 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, in order 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 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 placebo. Dizziness and somnolence were not significantly different between ibuprofen and placebo (Analysis 2.10). 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 above).

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 2 hours, both ibuprofen 200 mg or 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 headache free at 2 hours with 400 mg, 20% with 200 mg, and 11% with placebo. For headache relief at 2 hours, both ibuprofen 200 mg and 400 mg were significantly better than placebo, giving NNTs of 6.3 and 3.2, respectively; 57% of participants were headache free at 2 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 1 hour, the NNTs were 8.9 and 5.9 respectively, with no significant difference between doses; 35% of participants were headache free at 2 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, giving an NNT of 4; 45% of participants were headache free at 2 hours with 400 mg, and 19% with placebo. About one in three participants treated with ibuprofen 400 mg experienced headache relief at 1 hour, just over half experienced relief at 2 hours, and just under half sustained relief for 24 hours, but only around one in four or one in five were pain-free at 2 hours.

These results are similar to those found for aspirin 900 mg or 1000 mg in a separate Cochrane review (Kirthi 2010), with ibuprofen 400 mg performing slightly better than aspirin, and ibuprofen 200 mg slightly worse. In the Kirthi 2010 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 1 hour with ibuprofen 400 mg, there was a significant difference between soluble and standard formulations (P = 0.0114), but by 2 hours the difference was lost. This almost certainly reflects a faster uptake of the soluble formulation resulting in a more rapid effect, but by 2 hours the standard formulation had ’caught up’.

Fewer participants needed rescue medication with ibuprofen 200 mg (27%) or 400 mg (38%) than 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).

There was no significant difference between ibuprofen 400 mg and rofecoxib 25 mg for headache relief at 2 hours, 24-hour headache relief, and use of rescue medication. 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 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.

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 2 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 2 hours, and better relief of nausea, compared with aspirin alone (Kirthi 2010), 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, particularly for specific adverse events and for presence and relief of vomiting at 2 hours.

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 15 for pain-free at 2 hours, and 8 for headache relief at 2 hours; in both instances in excess of 2700 participants would have to have been involved in unpublished trials with zero treatment effects for the NNT to increase above the specified thresholds. This level of unpublished data is highly unlikely, so the results appear robust to the threat of publication bias.

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 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 included 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, but provides complete headache relief within 2 hours in 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 2 hours. Soluble formulations gave significantly better results for headache relief at 1 and 2 hours. No increase in number 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 ibuprofen compared to triptans and other OTC analgesics, such as aspirin and paracetamol, and to establish the efficacy of ibuprofen lysine. 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 give better relief of nausea and vomiting, and may also improve headache relief.

Acknowledgments

SOURCES OF SUPPORT

Internal sources

- Oxford Pain Research Funds, UK.

External sources

- NHS Cochrane Collaboration Programme Grant Scheme, UK.
- NIHR Biomedical Research Centre Programme, UK.

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

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	"computer-generated randomization code"
Allocation concealment?	Yes	"unopened treatment-blinding tear-off portion of winged label was affixed to the patient's case report form"
Blinding? All outcomes	Yes	All participants "received a blister card containing two tablets that were identical in colour, size, and shape"

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: 1-6 attacks/month in previous year N = 312 (cross-over trial, 882 attacks)

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	M 59, F 253 Mean age 38 years History of aura: 21%
Interventions	Ibuprofen 400 mg, n = 212 ASA 2 × 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

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	"predetermined randomization code"
Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	Yes	"double-dummy" method with "matching placebo" for each treatment

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

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not reported
Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	Yes	" identically-appearing placebo"

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 × 200 mg, n = 669 Paracetamol + aspirin + caffeine 2 × 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

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not described
Allocation concealment?	Unclear	Not described
Blinding? All outcomes	Yes	Double-dummy method

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 12-19 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

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not reported
Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	Yes	"matching placebo"

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 hx 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

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	"random number tables"
Allocation concealment?	Unclear	Randomisation done by one investigator and responses evaluated by the other, but no details about method of concealment
Blinding? All outcomes	Unclear	Tablets had identical packets, but were not identical in appearance

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/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

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	"computer-generated random numbers"
Allocation concealment?	Unclear	Randomisation done by one investigator and responses evaluated by the other, but no details about method of concealment
Blinding? All outcomes	Unclear	Medication "provided in identical packets"

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, 2-6 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

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not specified

Allocation concealment?	Unclear	Not specified
Blinding? All outcomes	Yes	“identical sachets”

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: 1-8 migraine attacks/month in the 6 months prior to 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

Item	**Authors’ judgement**	**Description**
Adequate sequence generation?	Yes	“computer generated randomization schedule”
Allocation concealment?	Yes	Remote allocation
Blinding? All outcomes	Yes	Placebo tablets visually matched the three active treatments

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 ± 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 1 hour	2	777	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [1.15, 1.83]
3 Headache relief at 2 hours	2	777	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [1.17, 1.61]
4 Participants using rescue medication	2	777	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.58, 0.86]
5 Any adverse event within 24 hours	2	780	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.67, 1.08]
6 Relief of associated symptoms at 2h	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 Presence of associated symptoms at 2 hours	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Nausea	2	776	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.71, 1.06]
7.2 Photophobia	2	751	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [1.05, 1.85]
7.3 Phonophobia	2	777	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.82, 0.98]
7.4 Functional disability	2	777	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.75, 0.92]
8 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 1 hour	4	1269	Risk Ratio (M-H, Fixed, 95% CI)	1.89 [1.54, 2.30]
2.1 Standard formulation	2	878	Risk Ratio (M-H, Fixed, 95% CI)	1.75 [1.34, 2.27]
2.2 “Soluble” formulation	2	391	Risk Ratio (M-H, Fixed, 95% CI)	2.12 [1.55, 2.89]
3 Headache relief at 2 hours	7	1815	Risk Ratio (M-H, Fixed, 95% CI)	2.17 [1.92, 2.45]
3.1 Standard formulation	5	1424	Risk Ratio (M-H, Fixed, 95% CI)	2.49 [2.12, 2.91]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2 “Soluble” formulation	2	391	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [1.32, 1.92]
4 Sustained headache relief over 24 hours	4	879	Risk Ratio (M-H, Fixed, 95% CI)	2.17 [1.76, 2.69]
5 Participants using rescue medication	7	1815	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.61, 0.74]
6 Any adverse event within 24 hours	7	2656	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.82, 1.15]
7 Relief of associated symptoms at 2 h	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Nausea	3	634	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [1.27, 1.86]
7.2 Vomiting	2	93	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [1.21, 1.92]
7.3 Photophobia	4	1328	Risk Ratio (M-H, Fixed, 95% CI)	1.51 [1.29, 1.77]
7.4 Phonophobia	4	1261	Risk Ratio (M-H, Fixed, 95% CI)	1.63 [1.39, 1.90]
8 Presence of associated symptoms at 2 hours	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Nausea	3	1153	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.60, 0.85]
8.2 Vomiting	2	810	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.08, 0.69]
8.3 Photophobia	4	1587	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.77, 0.90]
8.4 Phonophobia	4	1587	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.71, 0.85]
9 Relief of functional disability at 2 hours	3	1114	Risk Ratio (M-H, Fixed, 95% CI)	1.61 [1.38, 1.89]
10 Specific adverse events	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 Nausea	7	2297	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.54, 1.00]
10.2 Abdominal pain	6	2230	Risk Ratio (M-H, Fixed, 95% CI)	2.36 [1.12, 4.96]
10.3 Dizziness	3	1615	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.46, 2.22]
10.4 Somnolence	4	1717	Risk Ratio (M-H, Fixed, 95% CI)	2.53 [0.79, 8.17]

Comparison 3
Ibuprofen 400 mg versus rofecoxib 25 mg

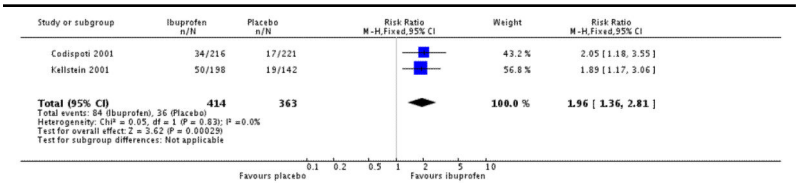
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Headache relief at 2 hours	2	444	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.85, 1.17]
2 Sustained headache relief over 24 hours	2	444	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.66, 1.10]
3 Participants using rescue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

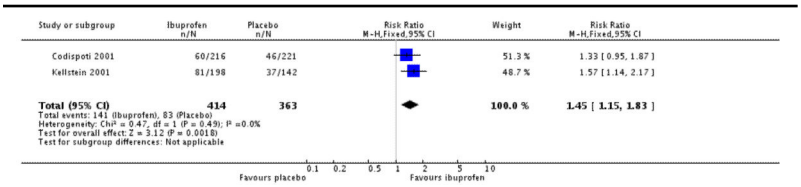
Analysis 1.1
Comparison 1 Ibuprofen 200 mg versus placebo, Outcome 1 Pain-free at 2 hours

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



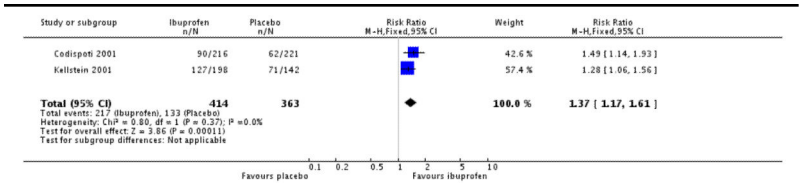
Analysis 1.2
Comparison 1 Ibuprofen 200 mg versus placebo, Outcome 2 Headache relief at 1 hour

Review: Ibuprofen with or without an antiemetic for acute migraine headaches in adults
Comparison: 1 Ibuprofen 200 mg versus placebo
Outcome: 2 Pain-free at 1 hours



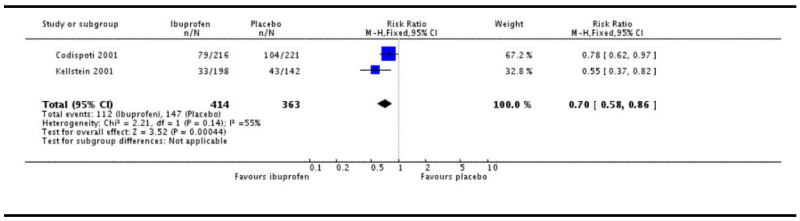
Analysis 1.3
Comparison 1 Ibuprofen 200 mg versus placebo, Outcome 3 Headache relief at 2 hours

Review: Ibuprofen with or without an antiemetic for acute migraine headaches in adults
Comparison: 1 Ibuprofen 200 mg versus placebo
Outcome: 3 Headache relief at 2 hours



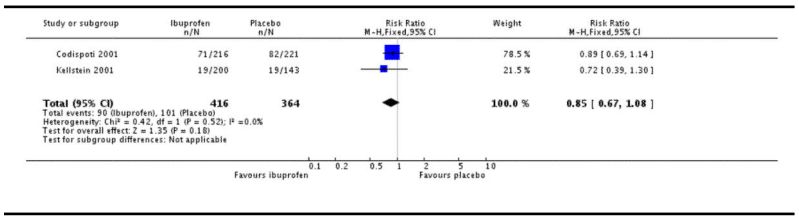
Analysis 1.4
Comparison 1 Ibuprofen 200 mg versus placebo, Outcome 4 Participants using rescue medication

Review: Ibuprofen with or without an antiemetic for acute migraine headaches in adults
Comparison: 1 Ibuprofen 200 mg versus placebo
Outcome: 4 Participants using rescue medication



Analysis 1.5
Comparison 1 Ibuprofen 200 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: 1 Ibuprofen 200 mg versus placebo
Outcome: 5 Any adverse event within 24 hours



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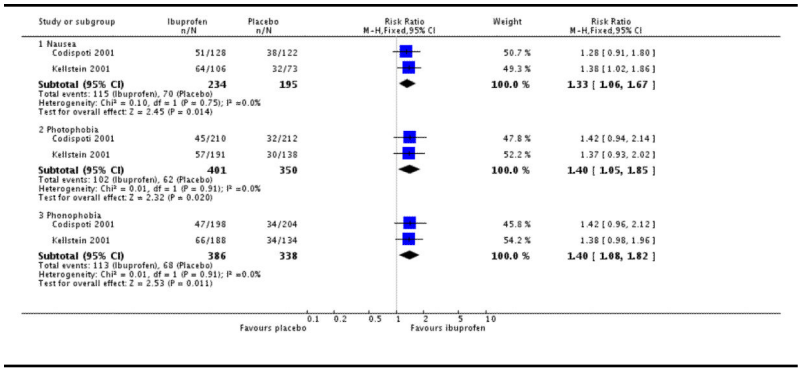
Analysis 1.6

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



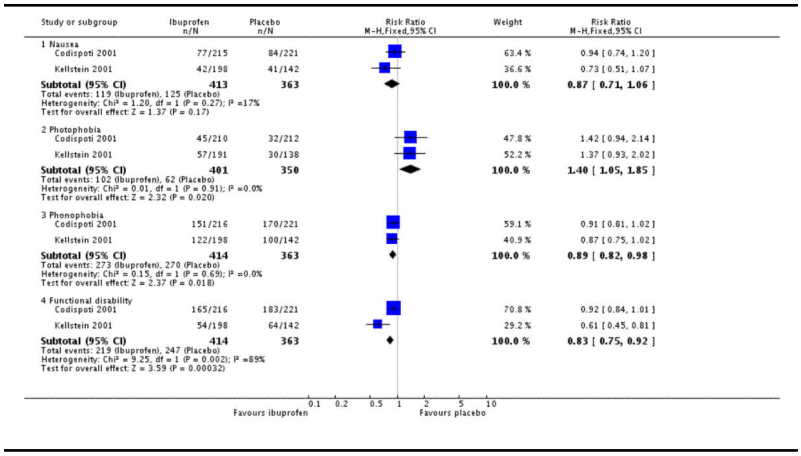
Analysis 1.7

Comparison 1 Ibuprofen 200 mg versus placebo, Outcome 7 Presence of associated symptoms 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 Presence of associated symptoms at 2 hours



Analysis 1.8

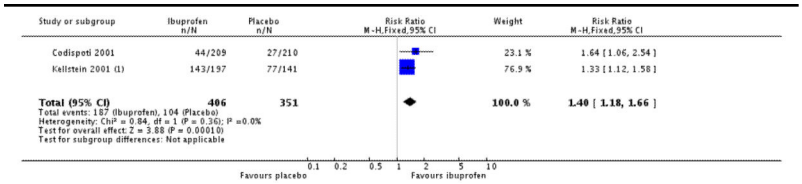
Comparison 1 Ibuprofen 200 mg versus placebo,

Outcome 8 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: 3 Relief of functional disability at 2 hours



(1) Reduced to none or mild

Analysis 2.1

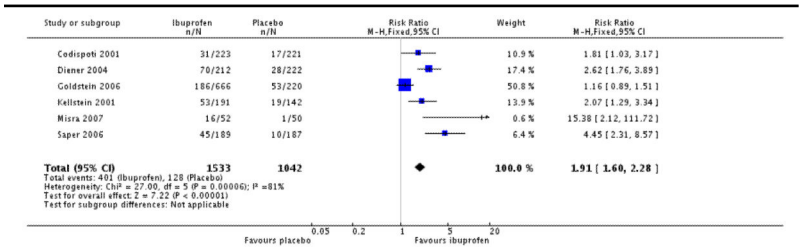
Comparison 2 Ibuprofen 400 mg versus placebo,

Outcome 1 Pain-free at 2 hours

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

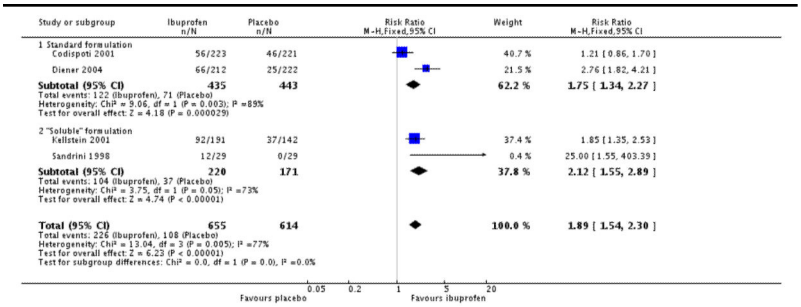
Comparison: 2 Ibuprofen 400 mg versus placebo

Outcome: 1 Pain-free at 2 hours



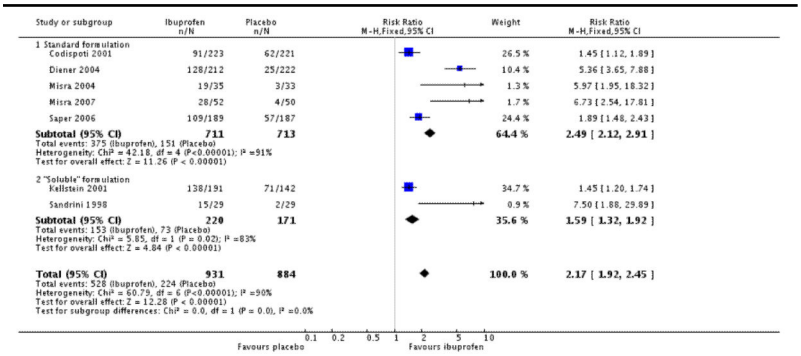
Analysis 2.2
Comparison 2 Ibuprofen 400 mg versus placebo, Outcome 2 Headache relief at 1 hour

Review: Ibuprofen with or without an antiemetic for acute migraine headaches in adults
Comparison: 2 Ibuprofen 400 mg versus placebo
Outcome: 2 Headache relief at 1 hour



Analysis 2.3
Comparison 2 Ibuprofen 400 mg versus placebo, Outcome 3 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: 3 Headache relief at 2 hours



Analysis 2.4

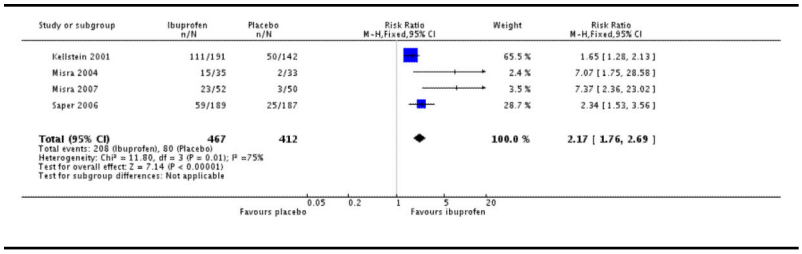
Comparison 2 Ibuprofen 400 mg versus placebo,

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



Analysis 2.5

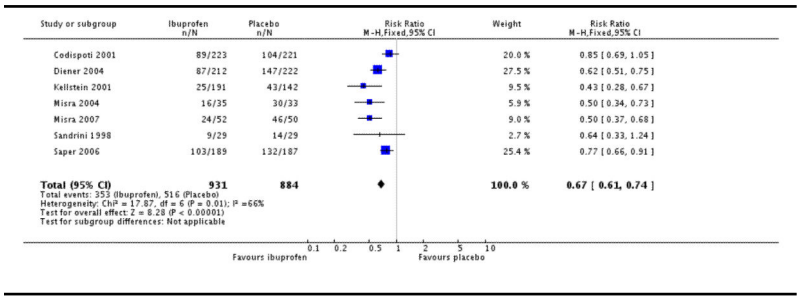
Comparison 2 Ibuprofen 400 mg versus placebo,

Outcome 5 Participants using rescue medication

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

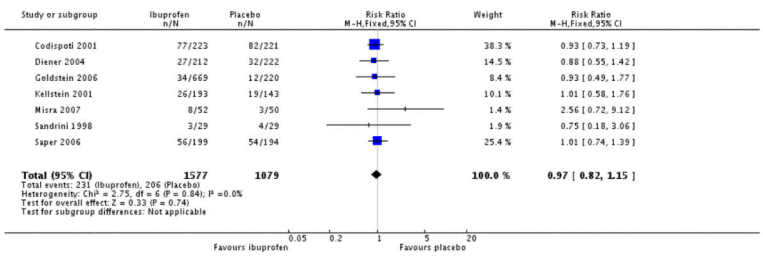
Comparison: 2 Ibuprofen 400 mg versus placebo

Outcome: 5 Participants using rescue medication



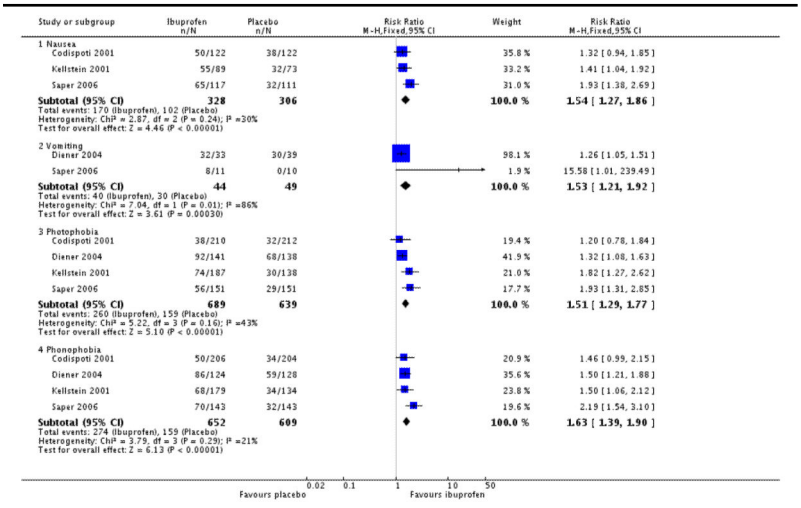
Analysis 2.6
Comparison 2 Ibuprofen 400 mg versus placebo, Outcome 6 Any adverse event within 24 hours

Review: Ibuprofen with or without an antiemetic for acute migraine headaches in adults
Comparison: 2 Ibuprofen 400 mg versus placebo
Outcome: 6 Any adverse event within 24 hours



Analysis 2.7
Comparison 2 Ibuprofen 400 mg versus placebo, Outcome 7 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: 7 Relief of associated symptoms at 2 h



Analysis 2.8

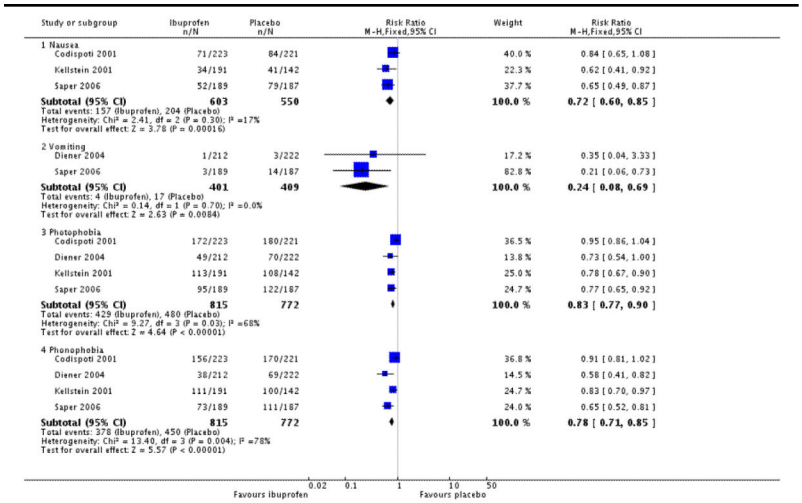
Comparison 2 Ibuprofen 400 mg versus placebo,

Outcome 8 Presence of associated symptoms at 2 hours

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

Comparison: 2 Ibuprofen 400 mg versus placebo

Outcome: 8 Presence of associated symptoms at 2 hours



Analysis 2.9

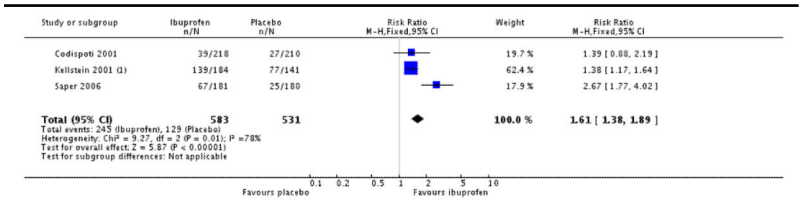
Comparison 2 Ibuprofen 400 mg versus placebo,

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

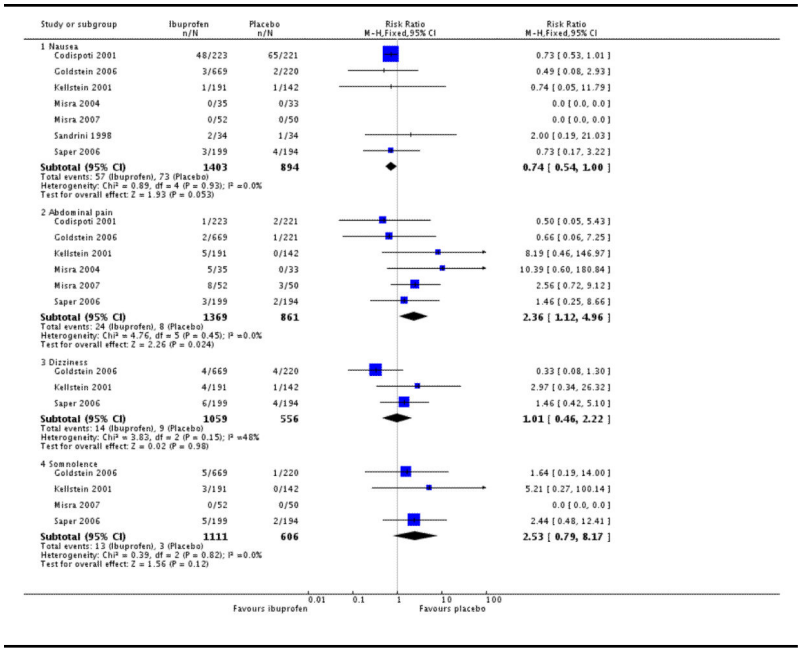
Outcome: 9 Relief of functional disability at 2 hours



(1) Reduced to none or mild

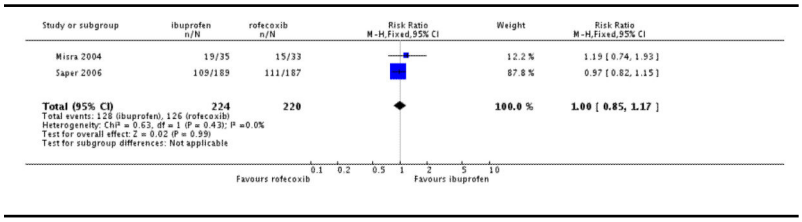
Analysis 2.10
Comparison 2 Ibuprofen 400 mg versus placebo, Outcome 10 Specific adverse events

Review: Ibuprofen with or without an antiemetic for acute migraine headaches in adults
Comparison: 2 Ibuprofen 400 mg versus placebo
Outcome: 10 Specific adverse events



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

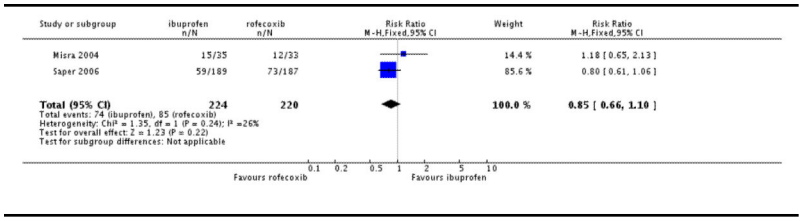
Review: Ibuprofen with or without an antiemetic for acute migraine headaches in adults
Comparison: 3 Ibuprofen 400 mg versus rofecoxib 25 mg
Outcome: 1 Headache relief at 2 hours



Analysis 3.2

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

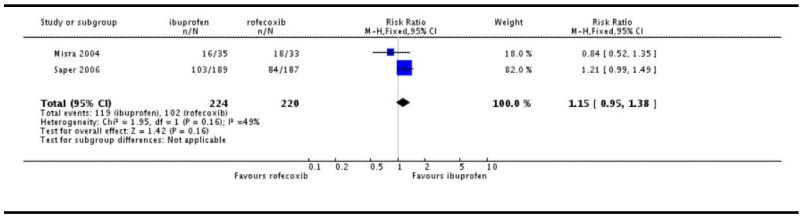
Review: Ibuprofen with or without an antiemetic for acute migraine headaches in adults
Comparison 3 Ibuprofen 400 mg versus rofecoxib 25 mg
Outcome: 2 Sustained headache relief over 24 hours



Analysis 3.3

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

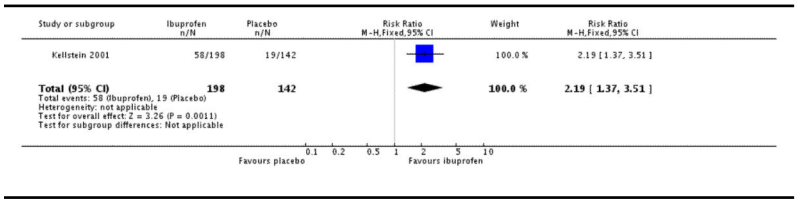
Review: Ibuprofen with or without an antiemetic for acute migraine headaches in adults
Comparison: 3 Ibuprofen 400 mg versus rofecoxib 25 mg
Outcome: 3 Participants using rescue medication



Analysis 4.1

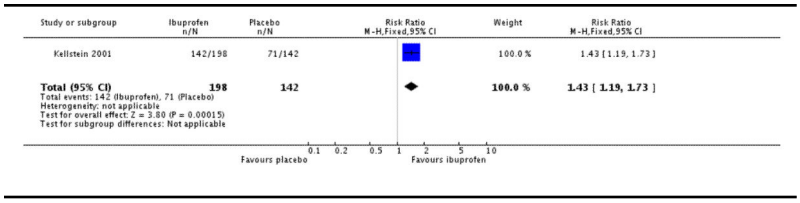
Comparison 4 Ibuprofen 600 mg versus placebo, Outcome 1 Pain-free at 2 hours

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



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



HISTORY

Protocol first published: Issue 4, 2009

Review first published: Issue 10, 2010

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have 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 2 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.

Appendix 1. 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 2. 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 3. 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 4. Summary of efficacy outcomes: headache relief, pain-free, and use of rescue medication

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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 = 221	(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
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 (3) Ibuprofen liquigel 600 mg, n = 198 (4) Placebo, n = 142	(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
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 5. Summary of efficacy outcomes: migraine-associated symptoms and functional disability

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Study ID	Treatment	Nausea		Vomitting		Photophobia		Phonophobia		Functional disability	
		Any at 2h	Relief at 2h	Any at 2h	Relief at 2h	Any at 2h	Relief at 2h	Any at 2h	Relief at 2h	Any at 2h	Relief at 2h
Codispoti 2001	(1) Ibuprofen 200 mg, n = 216 (2) Ibuprofen 400 mg, n = 223 (3) Placebo, n = 221	(1) 77/215 (2) 72/223 (3) 84/221	(1) 51/128 (2) 50/122 (3) 38/122	No usable data	No usable data	(1) 165/216 (2) 172/223 (3) 180/221	(1) 45/210 (2) 38/210 (3) 32/212	(1) 151/216 (2) 156/223 (3) 170/221	(1) 47/198 (2) 50/206 (3) 34/204	(1) 165/216 (2) 179/223 (3) 183/221	(1) 44/209 (2) 39/218 (3) 27/210
Diener 2004	(1) Ibuprofen 400 mg, n = 212 (2) Aspirin 1000 mg, n = 222 (3) Sumatriptan 50 mg, n = 226 (4) Placebo, n = 222	No usable data	No usable data	(1) 1/212 (2) 2/222 (3) 9/226 (4) 3/222	(1) 32/33 (2) 33/35 (3) 30/39 (4) 30/33	(1) 49/212 (2) 56/222 (3) 44/226 (4) 70/222	(1) 92/141 (2) 90/146 (3) 104/148 (4) 68/138	(1) 38/212 (2) 47/222 (3) 43/226 (4) 69/222	(1) 86/124 (2) 83/130 (3) 86/129 (4) 59/128	No data	No data
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									
Goldstein 2006	(1) Ibuprofen 400 mg, n = 669 (2) Paracetamol/ aspirin/caffeine 500/500/130 mg, n = 669 (3) Placebo, n = 221	Proportion of participants free of migraine-associated symptoms (functional disability, nausea, photophobia and phonophobia) significantly higher for ibuprofen than placebo at most time points									
Kellstein 2001	(1) Ibuprofen liquigel 200 mg, n = 198 (2) Ibuprofen liquigel 400 mg, n = 191 (3) Ibuprofen liquigel 600 mg, n = 198 (4) Placebo, n = 142	(1) 42/198 (2) 34/191 (3) 50/198 (4) 41/143	(1) 64/106 (2) 55/89 (3) 59/109 (4) 32/73	No data	No data	(1) 134/198 (2) 113/191 (3) 120/198 (4) 108/142	(1) 57/191 (2) 74/187 (3) 74/194 (4) 30/138	(1) 122/198 (2) 111/191 (3) 116/198 (4) 100/142	(1) 66/188 (2) 68/179 (3) 75/191 (4) 34/134	> mild (1) 54/198 (2) 45/191 (3) 53/198 (4) 64/142	(1) 143/197 (2) 139/184 (3) 140/193 (4) 77/141

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Study ID	Treatment	Nausea		Vomitting		Photophobia		Phonophobia		Functional disability	
		Any at 2h	Relief at 2h	Any at 2h	Relief at 2h	Any at 2h	Relief at 2h	Any at 2h	Relief at 2h	Any at 2h	Relief at 2h
Misra 2004	(1) Ibuprofen 400 mg, n = 40 (2) Rofecoxib 25 mg, n = 42 (3) Placebo, n = 42	No usable data: ~90% of participants had associated symptoms at baseline. Significantly more participants had relief of associated symptoms with ibuprofen 400 mg (~50%) and rofecoxib 25 mg (~40%) than placebo (~10%)								No data	No data
Misra 2007	(1) Ibuprofen 400 mg, n = 55 (2) Rizatriptan 10 mg, n = 57 (3) Placebo, n = 53	Significant mean improvement in associated symptoms and functional disability with ibuprofen 400 mg compared to placebo at 2 hours									
Sandrini 1998	(1) Ibuprofen arginine 400 mg, n = 34 (2) Placebo, n = 34	No data									
Saper 2006	Ibuprofen 400 mg, n = 199 Rofecoxib 25 mg, n = 194 Rofecoxib 50 mg, n = 196 Placebo, n = 194	(1) 52/189 (2) 58/187 (3) 56/188 (4) 79/187	(1) 65/117 (2) 51/109 (3) 73/129 (4) 32/111	(1) 3/189 (2) 5/187 (3) 11/188 (4) 14/187	(1) 8/11 (2) 7/12 (3) 3/14 (4) 0/187*	(1) 95/189 (2) 96/187 (3) 93/188 (4) 122/187	(1) 56/151 (2) 60/156 (3) 58/151 (4) 29/151	(1) 73/189 (2) 81/187 (3) 80/188 (4) 111/187	(1) 70/143 (2) 50/131 (3) 62/142 (4) 32/143	(1) 114/189 (2) 119/187 (3) 120/188 (4) 155/187	(1) 67/181 (2) 61/180 (3) 63/183 (4) 25/180**

* Increase of 4 participants with vomiting between baseline and 2 hours

** Increase of 3 participants with severe functional disability between baseline and 2 hours

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Appendix 6. Summary of outcomes: adverse events and withdrawals

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Study ID	Treatment	Any AE	Specific AEs	Serious AEs	AE withdrawal	Other withdrawals/exclusions
Codispoti 2001	(1) Ibuprofen 200 mg, n = 216 (2) Ibuprofen 400 mg, n = 223 (3) Placebo, n = 221	(1) 71/216 (2) 77/223 (3) 82/221	Commonly reported "drug-related AEs": Abdominal pain (1) 3, (2) 1, (3)2 Nausea (1) 53, (2) 48, (3) 65 Vomiting (1) 9, (2) 10, (3) 20	None	(1) 0/216 (2) 2/223 (3) 3/221 All nausea or vomiting	None
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 liquigel 400 mg, n = 191 (3) Ibuprofen liquigel 600 mg, n = 198 (4) Placebo, n = 142	(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 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	None	None	None
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

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Study ID	Treatment	Any AE	Specific AEs	Serious AEs	AE withdrawal	Other withdrawals/exclusions
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. Associated symptoms: symptom present 2 hours after taking study medication

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Summary of results B: symptom present 2 hours after taking study medication						
Intervention	**Studies**	**Participants**	**Treatment (%)**	**Placebo (%)**	**RR (95% CI)**	**NNTp (95% CI)**
Nausea						
Ibuprofen 200 mg versus placebo	2	776	29	34	0.87 (0.71 to 1/07)	18 (8.2 to 107)
Ibuprofen 400 mg versus placebo	3	1153	26	37	0.72 (0.61 to 0.85)	9.1 (6.1 to 18)
Vomiting						
Ibuprofen 400 mg versus placebo	2	810	1.0	4.2	0.24 (0.08 to 0.70)	32 (19 to 100)
Photophobia						
Ibuprofen 200 mg versus placebo	2	777	72	79	0.92 (0.85 to 1.00)	14 (7.6 to 89)
Ibuprofen 400 mg versus placebo	4	1587	53	62	0.83 (0.77 to 0.90)	10 (7.0 to 21)
Phonophobia						
Ibuprofen 200 mg versus placebo	2	777	66	74	0.89 (0.81 to 0.98)	12 (6.7 to 49)
Ibuprofen 400 mg versus placebo	4	1587	46	58	0.78 (0.71 to 0.85)	8.4 (6.0 to 14)
Functional disability						
Ibuprofen 200 mg versus placebo	2	777	53	68	0.83 (0.75 to 0.92)	6.6 (4.6 to 12)
Ibuprofen 400 mg versus placebo	3	1153	44	63	0.73 (0.66 to 0.81)	5.5 (4.2 to 7.9)

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. [PubMed: 11554954]

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. [PubMed: 15482357]

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. [PubMed: 8427430]

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. [PubMed: 16618262]

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. [PubMed: 15579612]

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. [PubMed: 17563841]

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. [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. [PubMed: 16492236]

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. [PubMed: 2676908]

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. [PubMed: 19920719]

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. [PubMed: 1623513]

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. [PubMed: 8706118]

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

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. [PubMed: 18711108]

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; (4) DOI: 10.1002/14651858.CD004604.pub3.

Clarke 1996 . Clarke CE, MacMillan L, Sondhi S, Wells NEJ. Economic and social impact of migraine. The Quarterly Journal of Medicine. 1996; 89(1):77–84.

Cook 1995 . Cook RJ, Sackett DL. The number needed to treat: a clinically useful measure of treatment effect. BMJ. 1995; 310(6977):452–4. [PubMed: 7873954]

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; (3) DOI: 10.1002/14651858.CD001548.pub2.

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. [PubMed: 17371352]

Edmeads 1993 . Edmeads J, Findlay H, Tugwell P, Pryse-Phillips W, Nelson RF, Murray TJ. Impact of migraine and tension-type headache on life-style, consulting behaviour, and medication use: a Canadian population survey. Canadian Journal of Neurological Sciences. 1993; 20(2):131–7. [PubMed: 8334575]

Ferrari 1998 . Ferrari MD. The economic burden of migraine to society. Pharmacoeconomics. 1998; 13(6):667–76. [PubMed: 10179702]

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. [PubMed: 15699376]

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. [PubMed: 18715330]

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. [PubMed: 18671771]

Hu 1999 . Hu XH, Markson LE, Lipton RB, Stewart WF, Berger ML. Burden of migraine in the United States: disability and economic costs. Archives of Internal Medicine. 1999; 159(8):813–8. [PubMed: 10219926]

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. [PubMed: 11167908]

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. [PubMed: 8880846]

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. [PubMed: 8721797]

Jhingran 1996 . Jhingran P, Cady RK, Rubino J, Miller D, Grice RB, Gutterman DL. Improvements in health-related quality of life with sumatriptan treatment for migraine. Journal of Family Practice. 1996; 42(1):36–42. [PubMed: 8537803]

Kirthi 2010 . 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. 2010; (4) DOI: 10.1002/14651858.CD008041.

L'Abbe 1987 . L'Abbé KA, Detsky AS, O'Rourke K. Meta-analysis in clinical research. Annals of Internal Medicine. 1987; 107(2):224–33. [PubMed: 3300460]

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. [PubMed: 17261680]

Lofland 1999 . Lofland JH, Johnson NE, Batenhorst AS, Nash DB. Changes in resource use and outcomes for patients with migraine treated with sumatriptan: a managed care perspective. Archives of Internal Medicine. 1999; 159(8):857–63. [PubMed: 10219932]

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. [PubMed: 16643573]

Moens 2007 . Moens G, Johannik K, Verbeek C, Bulterys S. The prevalence and characteristics of migraine among the Belgian working population. Acta Neurologica Belgica. 2007; 107(3):84–90. PUBMED: 18072336. [PubMed: 18072336]

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. [PubMed: 9870574]

Moore 2008 . Moore, RA.; Barden, J.; Derry, S.; McQuay, HJ. Managing potential publication bias. In: McQuay, HJ.; Kalso, E.; Moore, RA., editors. Systematic Reviews in Pain Research: Methodology Refined. IASP Press; Seattle: 2008. p. 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., editors. Statistics with confidence - confidence intervals and statistical guidelines. British Medical Journal; London: 1995. p. 50-63.

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. [PubMed: 12044621]

Osterhaus 1994 . Osterhaus JT, Townsend RJ, Gandek B, Ware JE Jr. Measuring the functional status and well-being of patients with migraine headache. Headache. 1994; 34(6):337–43. [PubMed: 7928312]

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. [PubMed: 19125877]

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. [PubMed: 6884416]

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. [PubMed: 19012253]

Solomon 1997 . Solomon GD, Price KL. Burden of migraine. A review of its socioeconomic impact. Pharmacoeconomics. 1997; 11(Suppl 1):1–10. [PubMed: 10168038]

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. [PubMed: 17878396]

Tramer 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. [PubMed: 9310564]

Volans 1974 . Volans GN. Absorption of effervescent aspirin during migraine. British Medical Journal. 1974; 4(5939):265–8. [PubMed: 4425854]

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. [PubMed: 791318]

* *Indicates the major publication for the study*

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PLAIN LANGUAGE SUMMARY

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

A single oral dose of ibuprofen 200 mg or 400 mg is effective in relieving pain, functional disability and associated symptoms of migraine headaches (nausea, vomiting, photophobia, phonophobia). Pain will be reduced from moderate or severe to no pain by 2 hours in just over 1 in 4 people (26%) taking ibuprofen 400 mg, compared with about 1 in 10 (12%) taking placebo. Pain will be reduced from moderate or severe to no worse than mild pain by 2 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 2 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.

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.

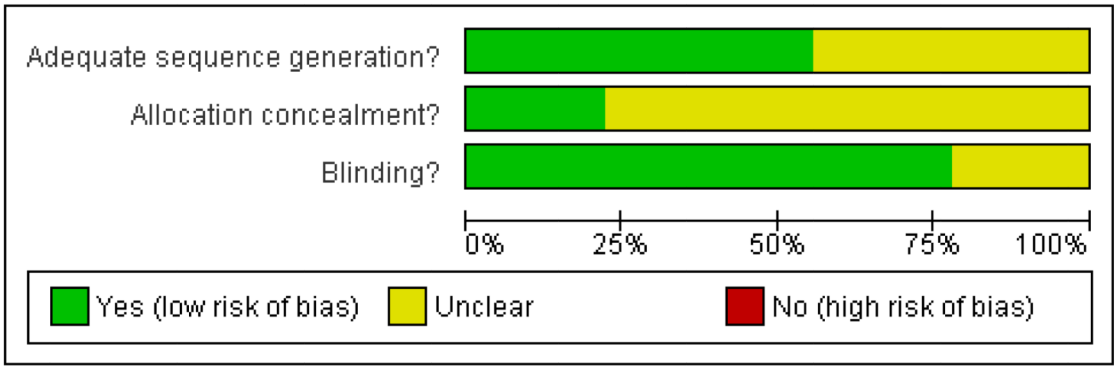

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies

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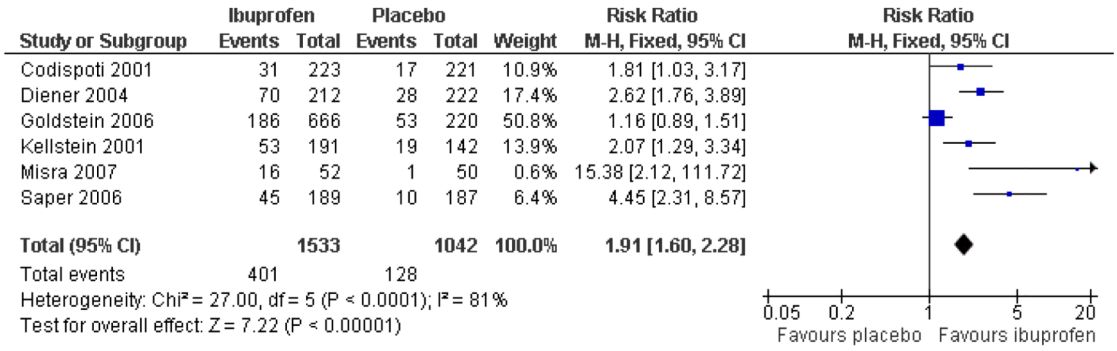

Figure 2. Forest plot of comparison: 2 Ibuprofen 400 mg versus placebo, outcome: 2.1 Pain-free at 2 hours

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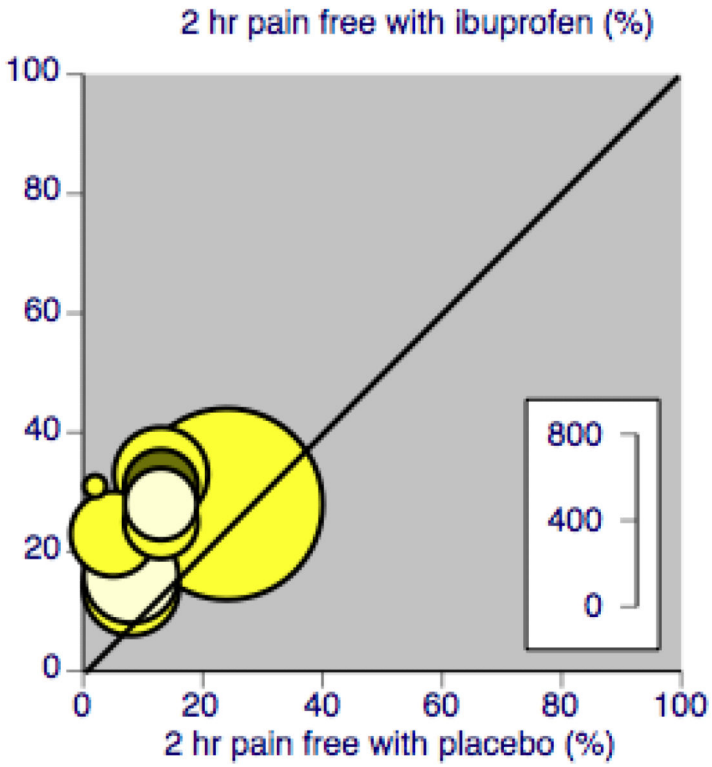

Figure 3. L'Abbe plot showing 2-hour pain-free response for ibuprofen versus placebo. Size of circle is proportional to size of study. Cream - 200 mg; Yellow - 400 mg; Brown - 600 mg ibuprofen

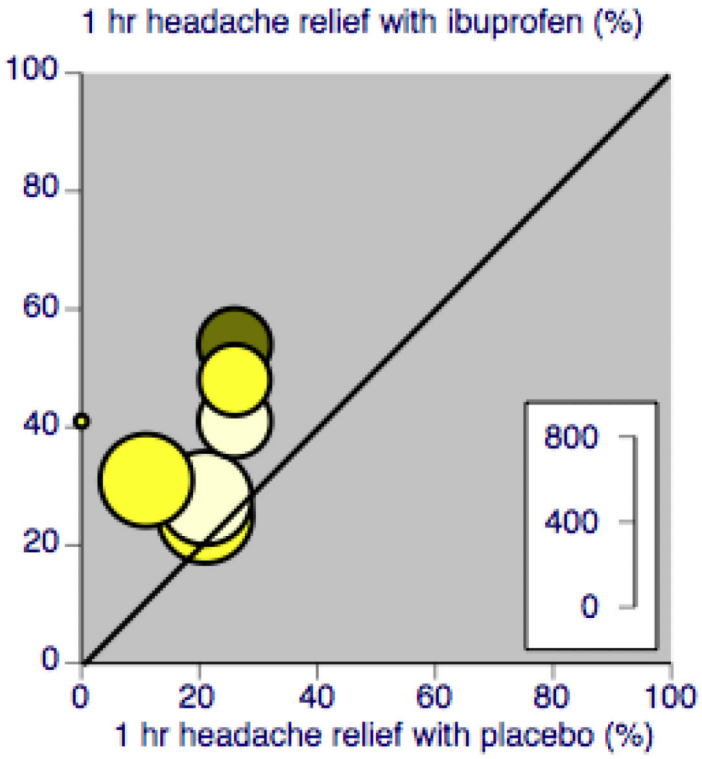

Figure 4. L'Abbe plot showing 1-hour headache relief for ibuprofen versus placebo. Size of circle is proportional to size of study. Cream - 200 mg; Yellow - 400 mg; Brown - 600 mg ibuprofen

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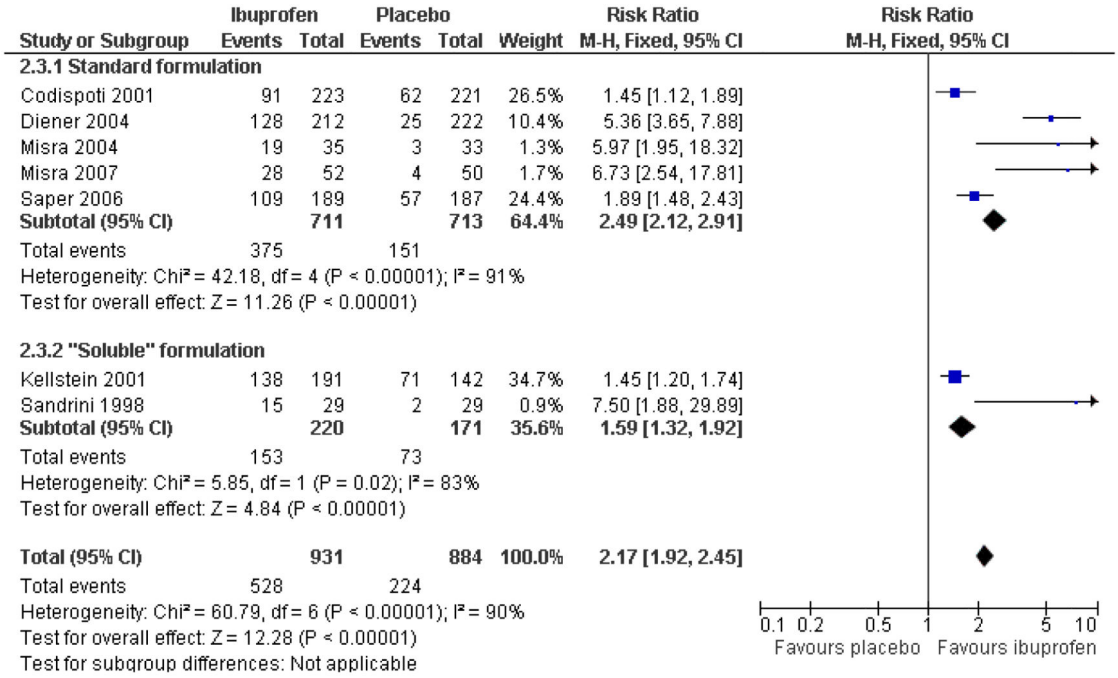

Figure 5. Forest plot of comparison: 2 Ibuprofen 400 mg versus placebo, outcome: 2.3 Headache relief at 2 hours

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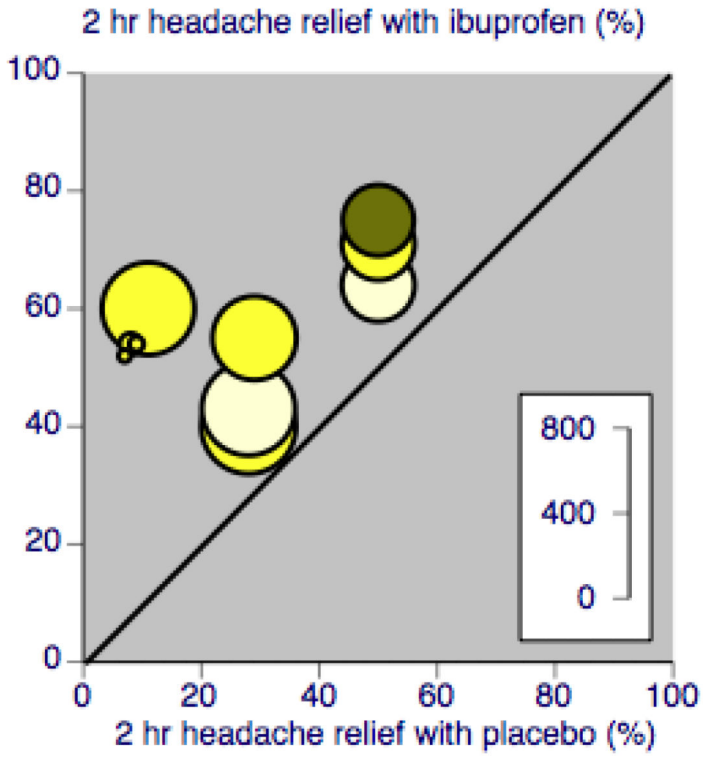

Figure 6. L'Abbe plot showing 2-hour headache relief for ibuprofen versus placebo. Size of circle is proportional to size of study. Cream - 200 mg; Yellow - 400 mg; Brown - 600 mg ibuprofen

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