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

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[Intervention Review]

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

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A B S T R A C T

Background

Migraine is a common, disabling condition and a burden for the individual, health services, and society. Many sufferers choose not to, or are unable to, seek professional help and rely on over-the-counter analgesics. Naproxen is a non-steroidal anti-inflammatory drug (NSAID); its efficacy in acute migraine has not been established by systematic reviews. Co-therapy with an antiemetic should help to reduce the nausea and vomiting commonly associated with migraine headaches.

Objectives

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

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) on *The Cochrane Library*, MEDLINE, EMBASE, and the Oxford Pain Relief Database, together with two online databases (www.gsk-clinicalstudyregister.com and www.clinicaltrials.gov) and reference lists, for studies to 22 May 2013.

Selection criteria

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

Data collection and analysis

Two review authors independently assessed trial quality and extracted data. We used numbers of participants achieving each outcome to calculate risk ratios and numbers needed to treat (NNT) or harm (NNH) compared with placebo or a different active treatment.

Main results

We included six studies using naproxen 275 mg, 500 mg, or 825 mg to treat attacks of moderate or severe pain intensity. Overall, 1241 participants took naproxen (275 mg to 825 mg), 229 took sumatriptan 50 mg, 173 took naratriptan 2.5 mg, and 1092 took placebo. No studies combined naproxen with an antiemetic. Studies using naproxen 275 mg provided no useable data for analysis.

Naproxen (500 mg and 825 mg) was better than placebo for pain-free response and headache relief. At two hours, the NNT for pain-free response was 11 (95% CI 8.7 to 17) (17% response with naproxen, 8% with placebo; risk ratio 2.0 (1.6 to 2.6), moderate quality) and for headache relief was 6.0 (4.8 to 7.9) (45% response with naproxen, 29% with placebo; risk ratio 1.6 (1.4 to 1.8), moderate quality). The NNT for sustained pain-free response during the 24 hours post dose was 19 (13 to 34) (12% response with naproxen, 6.7% with placebo), and

for sustained headache relief during the 24 hours post dose was 8.3 (6.4 to 12) (30% response with naproxen, 18% with placebo). Analysing only the lower dose of 500 mg of naproxen did not significantly change the results. Adverse events, which were mostly mild or moderate in severity and rarely led to withdrawal, were more common with naproxen than with placebo when the 500 mg and 825 mg doses were considered together, but not when the 500 mg dose was analysed alone.

There were insufficient data for analysis of naproxen compared with sumatriptan, and no data suitable for analysis of naproxen compared with naratriptan.

Authors' conclusions

Naproxen is statistically superior to placebo in the treatment of acute migraine, but the NNT of 11 for pain-free response at two hours suggests that it is not a clinically useful treatment. Cochrane reviews examining other commonly used analgesics for acute migraine have reported better (lower) NNT results for the same outcome. Naproxen is not clinically useful as a stand-alone analgesic in acute migraine, as it is effective in fewer than 2 people in 10.

P L A I N   L A N G U A G E   S U M M A R Y

Naproxen for acute migraine in adults

Migraine is a complex condition with a wide variety of symptoms. For many people the main feature is a painful headache. Other symptoms include feeling sick, vomiting, disturbed vision, and sensitivity to light, sound, and smells.

Non-steroidal anti-inflammatory drugs (NSAIDs) are used to treat migraine headaches. One NSAID is naproxen. On 22 May 2013, we looked for clinical trials where naproxen was used to treat migraine headache. We found six good quality studies with about 2700 people.

Naproxen was more effective than placebo for relieving migraine headache in adults, but only weakly so. From having headache pain described as moderate or severe, about 2 in 10 people (17%) were pain-free at two hours when treated with naproxen. However, about 1 in 10 (8%) were pain-free at two hours when treated with placebo. Almost 5 in 10 had some headache relief with naproxen, and 3 in 10 with placebo. Naproxen is not as good as some other medicines such as ibuprofen or sumatriptan. More dizziness, tingling sensations (paraesthesia), sleepiness (somnolence), nausea, indigestion (dyspepsia), dry mouth, and abdominal discomfort were reported with the 825 mg dose. These effects were generally of mild to moderate severity and rarely led to withdrawal from the studies.

Naproxen is not a good drug for treating migraine at the doses of 500 mg or 825 mg used in the studies we found.

SUMMARY OF FINDINGS

Summary of findings 1. Naproxen 500 mg or 825 mg compared with placebo for migraine headache

Naproxen 500 mg or 825 mg compared with placebo for migraine headache

Patient or population: migraine headache - moderate or severe pain

Settings: community

Intervention: naproxen 500 mg or 825 mg

Comparison: placebo

Outcomes	Probable outcome with comparator	Probable outcome with intervention	NNT or NNH and/ or relative effect (95% CI)	No of studies, attacks, events	Quality of the evidence (GRADE)	Comments
Pain-free response at 2 h	80 in 1000	170 in 1000	NNT 11 (8.7 to 17)	4 studies, 2149 attacks, 275 events	Moderate[1]	Lower NNTs are better than higher NNTs
Headache relief at 2 h	290 in 1000	450 in 1000	NNT 6.0 (4.8 to 7.9)	4 studies, 2149 attacks, 793 events	Moderate[1]	Lower NNTs are better than higher NNTs
Sustained pain-free during the 24 h post dose	70 in 1000	120 in 1000	NNT 19 (13 to 34)	4 studies, 2149 attacks, 202 events	Moderate[1]	Lower NNTs are better than higher NNTs
Sustained headache relief during the 24 h post dose	180 in 1000	300 in 1000	NNT 8.3 (6.4 to 12)	4 studies, 2149 attacks, 505 events	Moderate[1]	Lower NNTs are better than higher NNTs
At least one AE	120 in 1000	150 in 1000	NNH 28 (15 to 130)	4 studies, 2174 attacks, 293 events	Low[2]	Higher NNHs are better than lower NNTs
Serious AE	Insufficient data					-

AE: adverse event; **CI:** confidence interval; **NNT:** number needed to treat; **NNH:** number needed to harm.

Note: NNT or NNH is reported when an outcome is statistically different from placebo or comparator. Where the result is not statistically different, a risk ratio or similar outcome is reported.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

1 - Quality of evidence downgraded from high because of threat from potential publication bias with modest effect size and numbers of events.
2 - Quality of evidence downgraded from high because of threat from potential publication bias with modest effect size and numbers of events, combined with inconsistent reporting of the outcome.

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BACKGROUND

Description of the condition

Migraine is a common, disabling headache disorder, ranked seventh highest among specific causes of disability globally (Steiner 2013), and with considerable social and economic impact (Hazard 2009). Rcent reviews found a one-year prevalence of 15% globally (Vos 2012) and for adults in European countries (Stovner 2010), 13% for all ages in the USA (Victor 2010), 21% in Russia (Ayzenberg 2012), and 9% for adults in China (Yu 2012). Migraine is more prevalent in women than in men (by a factor of two to three), and in the age range 30 to 50 years.

The International Headache Society (IHS) classifies two major subtypes (IHS 2013). Migraine without aura is the most common subtype. It is characterised by attacks lasting 4 to 72 hours that are typically of moderate to severe pain intensity (PI), unilateral, pulsating, aggravated by normal physical activity, and associated with nausea with or without photophobia and phonophobia. Migraine with aura is characterised by reversible focal neurological symptoms that develop over a period of at least 5 minutes and last for less than 60 minutes, followed by headache with the features of migraine without aura. In some cases, the headache may lack migrainous features or be absent altogether (IHS 2013).

A large prevalence study in the USA 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 migraineurs (98%) used acute treatments for attacks, with 49% using over-the-counter (OTC) medication only, 20% using prescription medication, and 29% using both. OTC medication included aspirin, other non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol (acetaminophen), and paracetamol with caffeine (Bigal 2008; Diamond 2007; Lipton 2007). Similar findings have been reported from other large studies in France and Germany (Lucas 2006; Radtke 2009).

The significant impact of migraine with regard to pain, functional health, and well-being is well documented (Buse 2011; Leonardi 2005); it is ranked in the top 10 disorders for global years lived with disability (Vos 2012). A cross-sectional survey of eight EU countries (representing 55% of the adult population) has estimated an annual direct and indirect cost of migraine per person of EUR 1222, and a total annual cost for the EU of EUR 111 billion for adults aged 18 to 65 years (Linde 2012). Costs vary between countries, probably due to differences in available therapies and the way they are delivered, and structural differences in healthcare systems (Bloudek 2012). In the USA, the mean annual direct cost per person has been estimated at USD 1757 for episodic migraine and USD 7750 for chronic migraine (Munakata 2009). Whatever the exact direct and indirect costs are for each country, it is clear that migraine presents a significant economic burden. Successful treatment of acute migraine attacks not only benefits patients by reducing their disability and improving health-related quality of life, but also has the potential to reduce the need for healthcare resources and increase economic productivity.

Description of the intervention

Naproxen is an NSAID first marketed in the mid-1970s, with confirmed efficacy in acute (Derry 2009), and chronic (Moore 2010a; Moore 2010b) pain. It is a propionic acid derivative (of the same family as ibuprofen), with analgesic, anti-inflammatory, and antipyretic properties. It has been widely used in treating arthritis, menstrual cramps, gout, sprains and strains, and a variety of acute pain conditions. Naproxen and its soluble sodium salt are commonly available as 250 mg and 500 mg tablets (275 mg and 550 mg of sodium salt). In many parts of the world it remains a prescription-only drug, but in others such as the USA, UK, and most parts of Canada, it is available OTC in restricted doses.

OTC medications are less expensive, more accessible, and tend to have favourable safety profiles relative to many prescription treatments, although naproxen causes more serious gastrointestinal adverse events than ibuprofen, for example (Hernandez-Diaz 2000). Naproxen may be a useful alternative OTC treatment of migraine headache in individuals who do not tolerate or respond to commonly used aspirin and ibuprofen.

In order to establish whether naproxen 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 (PR). 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 headache 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, which are responsible for pain and inflammation. Naproxen inhibits both COX isoforms. Prostaglandins mediate a variety of physiological functions, including maintenance of the gastric mucosal barrier, regulation of renal blood flow, and regulation of endothelial tone, and they also play an important role in inflammatory and nociceptive processes. Naproxen is thought to inhibit central sensitisation by attenuating meningeal inflammation and preventing central sensitisation arising from glial cells in the brain stem. In one study, naproxen suppressed central trigeminal neurons in an animal model of intracranial pain (Jakubowski 2007).

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 seeks to determine whether treatment of acute migraine with naproxen plus an antiemetic is in any way superior to treatment with naproxen alone. In a recent review of aspirin with or without an antiemetic for acute migraine (Kirthi 2013), aspirin plus metoclopramide was significantly better than aspirin alone for headache relief and relief of nausea at two hours, but not for pain-free at two hours or sustained pain-free during the 24 hours post dose.

Why it is important to do this review

Naproxen has confirmed efficacy in a variety of acute pain situations, is widely available and relatively inexpensive, and it is important to know where it fits in the range of therapeutic options for migraine therapy. For many migraineurs, non-prescription therapies offer convenience and may be the only therapies available or affordable. This review is one of a series examining the efficacy of OTC treatments for migraine, including aspirin (Kirthi 2013), paracetamol (acetaminophen) (Derry 2013), and ibuprofen (Rabbie 2013), as well as oral sumatriptan (Derry 2012), which is available without prescription in some countries. Naproxen in combination with sumatriptan is the subject of a separate review (Law 2013).

O B J E C T I V E S

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

M E T H O D S

Criteria for considering studies for this review

Types of studies

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

Types of participants

Studies enrolled adults (at least 18 years of age) with episodic migraine. We used the definition of migraine specified by the IHS (IHS 1988; IHS 2004; IHS 2013), although we accepted diagnostic criteria equivalent to IHS 1988 where a specific reference was not provided. We excluded studies evaluating treatments for chronic migraine. There were no other restrictions on migraine frequency, duration, or type (with or without aura). We accepted studies

that included participants taking stable prophylactic therapy to reduce the frequency of migraine attacks. If reported, details on any prophylactic therapy prescribed or allowed are provided in the Characteristics of included studies table.

Types of interventions

We included studies that used a single dose of naproxen to treat a migraine headache episode when pain was of moderate to severe intensity, or investigated different dosing strategies or timing of the first dose in relation to headache intensity, or both. There were no restrictions on dose or route of administration.

Included studies could use either naproxen alone or naproxen plus an antiemetic. The antiemetic had to be taken either combined with naproxen in a single formulation or separately not more than 30 minutes before naproxen, and be self administered or possible to self administer (ie given by a nurse in clinic, but could be taken by the participant at home).

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

Types of outcome measures

In selecting the main outcome measures for this review, we considered scientific rigour, availability of data, and patient preferences. Patients with acute migraine headaches have rated complete PR, no headache recurrence, rapid onset of PR, 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), we considered the following main outcomes.

Primary outcomes

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

We would have collected data for pain-free and headache relief outcomes at one hour if reported and relevant, for example, if a fast-acting formulation of the intervention was tested.

Secondary outcomes

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

Other outcomes

We also collected data for a number of other outcomes, including:

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

PI or PR had to be measured by the participant (not the investigator or care giver). Pain measures accepted for the main efficacy outcomes were:

- PI: 4-point categorical scale, with wording equivalent to none, mild, moderate, and severe; or 100 mm visual analogue scale (VAS)), where less than 30 mm was considered equivalent to mild or no pain and 30 mm or greater equivalent to moderate or severe pain (Collins 1997);
- PR: 5-point categorical scale, with wording equivalent to none, a little, some, a lot, complete; or 100 mm VAS, where less than 30 mm was considered equivalent to none or a little, and 30 mm or greater equivalent to some, a lot, or complete.

We considered only data obtained directly from the participant.

Definitions of important terms, including all measured outcomes, are provided in Appendix 1.

Search methods for identification of studies

Electronic searches

We searched the following electronic databases.

- The Cochrane Central Register of Controlled Trials (CENTRAL), (*The Cochrane Library*), Issue 4 of 12, 2013.
- MEDLINE (via Ovid),1947 to 22 May 2013.
- EMBASE (via Ovid), 1974 to 22 May 2013.
- Oxford Pain Relief Database, searched on 22 May 2013 (Jadad 1996a).

See Appendix 2, Appendix 3, and Appendix 4 for the search strategies for CENTRAL, MEDLINE (via Ovid), and EMBASE (via Ovid), respectively.

We applied no language restrictions.

Searching other resources

We searched for additional studies in reference lists of retrieved studies and review articles, and in two clinical trials databases (www.clinicaltrials.gov and www.gsk-clinicalstudyregister.com). We did not search grey literature and short abstracts.

Data collection and analysis

Selection of studies

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

Data extraction and management

Two review authors independently extracted data from included studies using a standard data extraction form. We settled disagreements by discussion with a third review author. One review author entered data into Review Manager 5 (RevMan 2012).

Assessment of risk of bias in included studies

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

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

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

Measures of treatment effect

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

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

- when significantly fewer adverse outcomes occurred with naproxen than with control (placebo or active) we use the term the number needed to treat to prevent one event (NNTp).
- when significantly more adverse outcomes occurred with naproxen 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 was in cross-over studies; we planned to use only first-period data where possible, but no included studies used a cross-over design. Where there were substantial missing data in any study, we commented on this and performed sensitivity analyses to investigate their effect.

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

Assessment of heterogeneity

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

Assessment of reporting biases

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

Data synthesis

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

We calculated effect sizes and combined data for analysis only for comparisons and outcomes where there were at least two studies and 200 participants (Moore 1998). Relative risk of benefit ('relative benefit') or harm ('relative risk') was calculated with 95% confidence intervals (CIs) using a fixed-effect model (Morris 1995). We calculated NNT, NNTp, and NNH with 95% CIs using the pooled number of events by the method of Cook and Sackett (Cook 1995). We assumed a statistically significant difference from control when the 95% CI of the RR of benefit or harm did not include the number one.

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

We described data from comparisons and outcomes with only one study or fewer than 200 participants in the summary tables and text where appropriate for information and comparison, but we did not analyse these data quantitatively.

Subgroup analysis and investigation of heterogeneity

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

Sensitivity analysis

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

Summary of findings and assessment of the certainty of the evidence

R E S U L T S

Description of studies

Results of the search

After screening titles and abstracts of all records retrieved in the searches, we identified 20 potentially relevant completed studies. We found one further study that may be completed but for which there were no data (NCT01390324); details are in Characteristics of studies awaiting classification (Figure 1).

Figure 1. Study flow diagram.


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┌─────────────────────┐         ┌─────────────────────┐
│ 21 records          │         │ 1 study probably    │
│ identified after    │────────▶│ completed, but no   │
│ screening titles    │         │ data available      │
│ and abstracts       │         │ (identified through │
│                     │         │ clinical trial      │
│                     │         │ registration)       │
└─────────────────────┘         └─────────────────────┘
           │
           ▼
┌─────────────────────┐         ┌─────────────────────┐
│ 20 records          │         │ 14 records          │
│ retrieved as full   │────────▶│ excluded            │
│ texts               │         │                     │
└─────────────────────┘         └─────────────────────┘
           │
           ▼
┌─────────────────────┐
│ 6 records           │
│ included in review: │
│                     │
│  ● 3 primary        │
│    publications     │
│    (4 studies)      │
│  ● 1 secondary      │
│    publication      │
│  ● 2 clinical trial │
│    summaries        │
└─────────────────────┘
           │
           ▼
┌─────────────────────┐         ┌─────────────────────┐
│ 6 studies included  │         │ 2 studies did not   │
│ in review           │────────▶│ provide any         │
│                     │         │ usable data for     │
│                     │         │ analysis            │
└─────────────────────┘         └─────────────────────┘
           │
           ▼
┌─────────────────────┐
│ 4 studies included  │
│ in quantitative     │
│ analysis            │
│ (meta-analysis)     │
└─────────────────────┘
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Included studies

Six studies (with data reported in three primary publications and two clinical trial summaries) satisfied all inclusion criteria, and are included in this review (Brandes 2007 Study 1 Brandes 2007 Study 2; S2WA4003; S2WA4004; Smith 2005; Wentz 2008). A further publication (Landy 2007) provided data on functional disability for the studies in Brandes 2007 Study 1 and Brandes 2007 Study 2 that were not reported in the primary publication. All studies used a parallel-group design, and medication was to be taken orally when the PI was of at least moderate intensity. All placebo-controlled studies treated a single attack with a single dose of study medication, while the active-controlled studies treated multiple attacks over a 12-week period, each with a single dose of study medication. No studies employed multiple dosing strategies for individual attacks.

All studies were multicentre and diagnosed migraine (with or without aura) according to IHS criteria. Individuals with frequent migraine headaches (> six or eight attacks per month) were excluded. Most studies required that participants had previously tolerated treatment with an NSAID or had no contraindications, or both. In all studies, participants self treated their headaches at home. The mean age of participants ranged from 40 to 42 years, and between 81% and 91% were female. Participants were eligible for inclusion if they were using stable prophylactic medication in three studies (Brandes 2007 Study 1 Brandes 2007 Study 2; Smith 2005), but Wentz 2008 excluded participants if they had been using prophylactic medication within one month of the trial period. S2WA4003 and S2WA4004 did not mention prophylaxis, but it seems likely that it was not allowed. All studies had an appropriate washout period between any analgesic or other prohibited medication that might interfere with the results and study medication.

Three studies gave naproxen 500 mg (Brandes 2007 Study 1 Brandes 2007 Study 2; Smith 2005), two gave only 275 mg (S2WA4003; S2WA4004), while Wentz 2008 gave naproxen 825 mg as this is the recommended maximum dose in Europe for acute migraine treatment. Four studies compared naproxen with placebo (Brandes 2007 Study 1 Brandes 2007 Study 2; Smith 2005; Wentz 2008); three also included treatment arms using sumatriptan and sumatriptan plus naproxen (Brandes 2007 Study 1 Brandes 2007 Study 2; Smith 2005). One study compared placebo and naproxen with a novel COX-2 NSAID (GW406381) (Wentz 2008); this drug is not marketed, so results are not reported here. Two studies were head-to-head comparisons of a low dose (275 mg) of naproxen with naratriptan (S2WA4003; S2WA4004). No studies combined naproxen with an antiemetic.

In total, 1241 participants took naproxen (275 mg to 825 mg), 229 took sumatriptan 50 mg, 173 took naratriptan 2.5 mg, and 1092 took placebo. The number included in efficacy analyses was slightly lower because some participants were excluded from these analyses due to major protocol violations or because they reported no useful results. A further 735 participants took sumatriptan 85 mg, and 737 took a combination of sumatriptan 85 mg and naproxen 500 mg (Brandes 2007 Study 1; Brandes 2007 Study 2). Sumatriptan 85 mg is a dose used only in the context of this particular combination and is not otherwise available; a comparison of naproxen alone with sumatriptan plus naproxen is included in Law 2013.

The outcomes reported by individual studies are listed in the Characteristics of included studies table. All studies measured headache PI using a standard 4-point scale. The placebo-controlled studies evaluated pain-free response at two hours and sustained pain-free during the 24 hours post dose as the primary outcome measures. Wentz 2008 was concerned with the primary outcomes for the novel NSAID but the relevant primary outcome data for naproxen were available. Dichotomous data could also be extracted from all placebo-controlled studies for the secondary outcomes of headache relief at two hours and sustained headache relief during the 24 hours post dose. Wentz 2008 and Smith 2005 also provided usable data for headache relief at the earlier time of one hour post dose. Dichotomous data on the use of rescue medication were reported, as were numerical data on adverse events. Data on relief of associated symptoms were reported but not in a consistent way; only one study reported data for calculation of relief of vomiting (Wentz 2008), while specific relief of nausea, photophobia, and phonophobia were available from three out of the four placebo-controlled studies (Brandes 2007 Study 1; Brandes 2007 Study 2; Wentz 2008).

The two studies with only an active control (no placebo) reported PR at four hours only and did not provide any usable efficacy data (S2WA4003; S2WA4004).

Details of individual studies are in the Characteristics of included studies table.

Excluded studies

We excluded 14 studies. Details are in the Characteristics of excluded studies table.

Risk of bias in included studies

Methodological quality, assessed using the Oxford Quality Scale, was good in all studies. One study scored 5/5 (Wentz 2008), three scored 4/5 (S2WA4003; S2WA4004; Smith 2005), and two scored 3/5 (Brandes 2007 Study 1; Brandes 2007 Study 2). Points were lost due to failure to report adequately the method of randomisation or blinding, or both, although it is likely that these were satisfactory as the trials are recent and would have been carried out in dedicated clinical trial facilities. Full details are in the Characteristics of included studies table.

In addition, we created a Risk of bias table, which considered sequence generation, allocation concealment, blinding, incomplete outcome data, and study size (Figure 2). Only one study adequately reported the method of allocation concealment (Wentz 2008). No study had substantial amounts of missing data, and no study was considered to be at high risk of bias.

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

Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias): All outcomes
Blinding of outcome assessment (detection bias): All outcomes
Incomplete outcome data (attrition bias): All outcomes
Size

0%   25%   50%   75%   100%

█ Low risk of bias   ☐ Unclear risk of bias   ■ High risk of bias
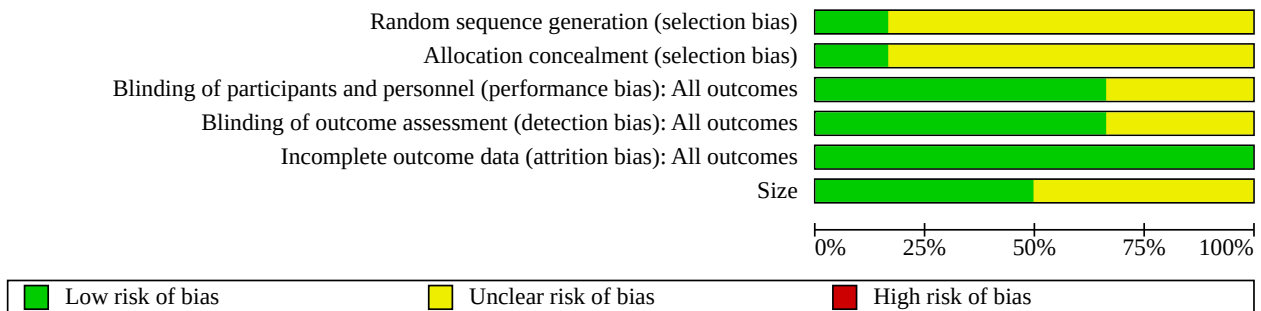
Effects of interventions

See: **Summary of findings 1** Naproxen 500 mg or 825 mg compared with placebo for migraine headache

The two active-controlled studies comparing naproxen 275 mg with naratriptan 2.5 mg did not report any of our prespecified efficacy outcomes (S2WA4003; S2WA4004); they did report numbers of participants experiencing our prespecified adverse event and withdrawal outcomes, but combined data for all attacks over a 12-week period without any explanation of how it was done, so we were unable to use them in analyses.

For analysis of the placebo-controlled studies, we chose to combine results from the three using naproxen 500 mg with the one using naproxen 825 mg. We carried out a sensitivity analysis to determine the effect of dose.

All included studies used one or more standard scales to measure PI or PR, and reported outcomes as defined in the Types of outcome measures section. Details of efficacy outcomes in individual studies are in Appendix 5 and of adverse events and withdrawals in Appendix 6.

Pain-free at two hours

Naproxen versus placebo

Four studies (2149 participants) provided data for use of naproxen, compared with placebo, when pain was moderate or severe (Brandes 2007 Study 1; Brandes 2007 Study 2; Smith 2005; Wentz 2008).

- The proportion of participants pain-free at two hours with naproxen 500/825 mg was 17% (183/1064; range 15% to 29%).
- The proportion of participants pain-free at two hours with placebo was 8.5% (92/1085; range 5.8% to 10%).
- The relative benefit of treatment compared with placebo was 2.0 (95% CI 1.6 to 2.6) (Figure 3); the NNT was 11 (8.7 to 17).
- For naproxen 500 mg alone, the NNT was 13 (9.7 to 22), which was not significantly different from the NNT for the combined dosage.

Figure 3. Forest plot of comparison: 1 Pain, outcome: 1.1 Pain-free response at two hours.

Study or Subgroup	Naproxen Events	Naproxen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Brandes 2007 Study 1	53	356	33	360	36.1%	1.62 [1.08 , 2.45]
Brandes 2007 Study 2	57	364	37	382	39.7%	1.62 [1.10 , 2.38]
Smith 2005	45	248	14	241	15.6%	3.12 [1.76 , 5.54]
Wentz 2008	28	96	8	102	8.5%	3.72 [1.78 , 7.75]
Total (95% CI)		**1064**		**1085**	**100.0%**	**2.03 [1.61 , 2.58]**
Total events:	183		92			

Heterogeneity: Chi² = 7.25, df = 3 (P = 0.06); I² = 59%
Test for overall effect: Z = 5.89 (P < 0.00001)
Test for subgroup differences: Not applicable

0.2   0.5   1   2   5
Favours placebo   Favours naproxen

The L'Abbé plot showed a considerable degree of similarity of response between different studies (Figure 4).

Figure 4. L'Abbé plot for pain-free response at two hours. Size of circle proportional to size of study (see inset scale). Cream = naproxen 500 mg, blue = naproxen 825 mg.

Naproxen versus sumatriptan 50 mg

One study compared naproxen 500 mg with sumatriptan 50 mg (474 participants) (Smith 2005); 45/248 (18%) were pain-free at two hours with naproxen 500 mg compared with 45/226 (20%) with sumatriptan 50 mg. There were insufficient data for analysis.
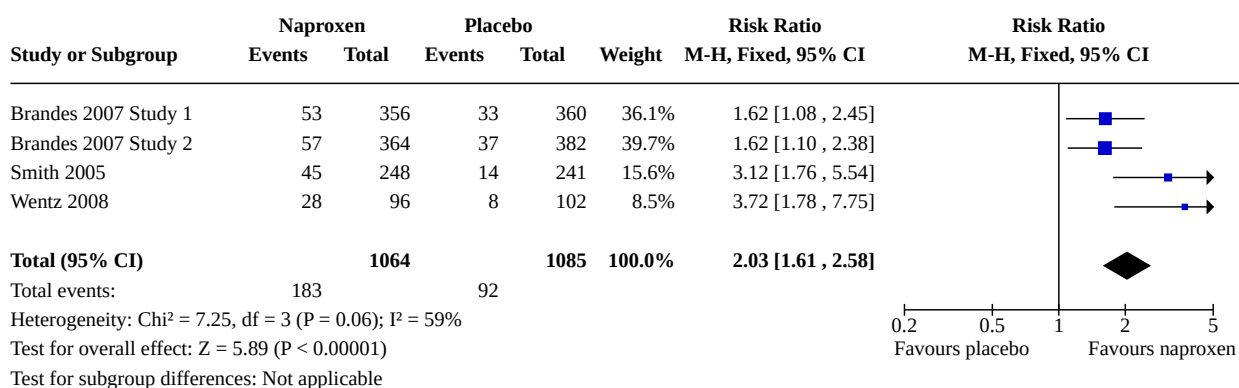
Headache relief at two hours

Naproxen versus placebo

Four studies (2149 participants) provided data for use of naproxen compared with placebo when pain was moderate or severe (Brandes 2007 Study 1; Brandes 2007 Study 2; Smith 2005; Wentz 2008).
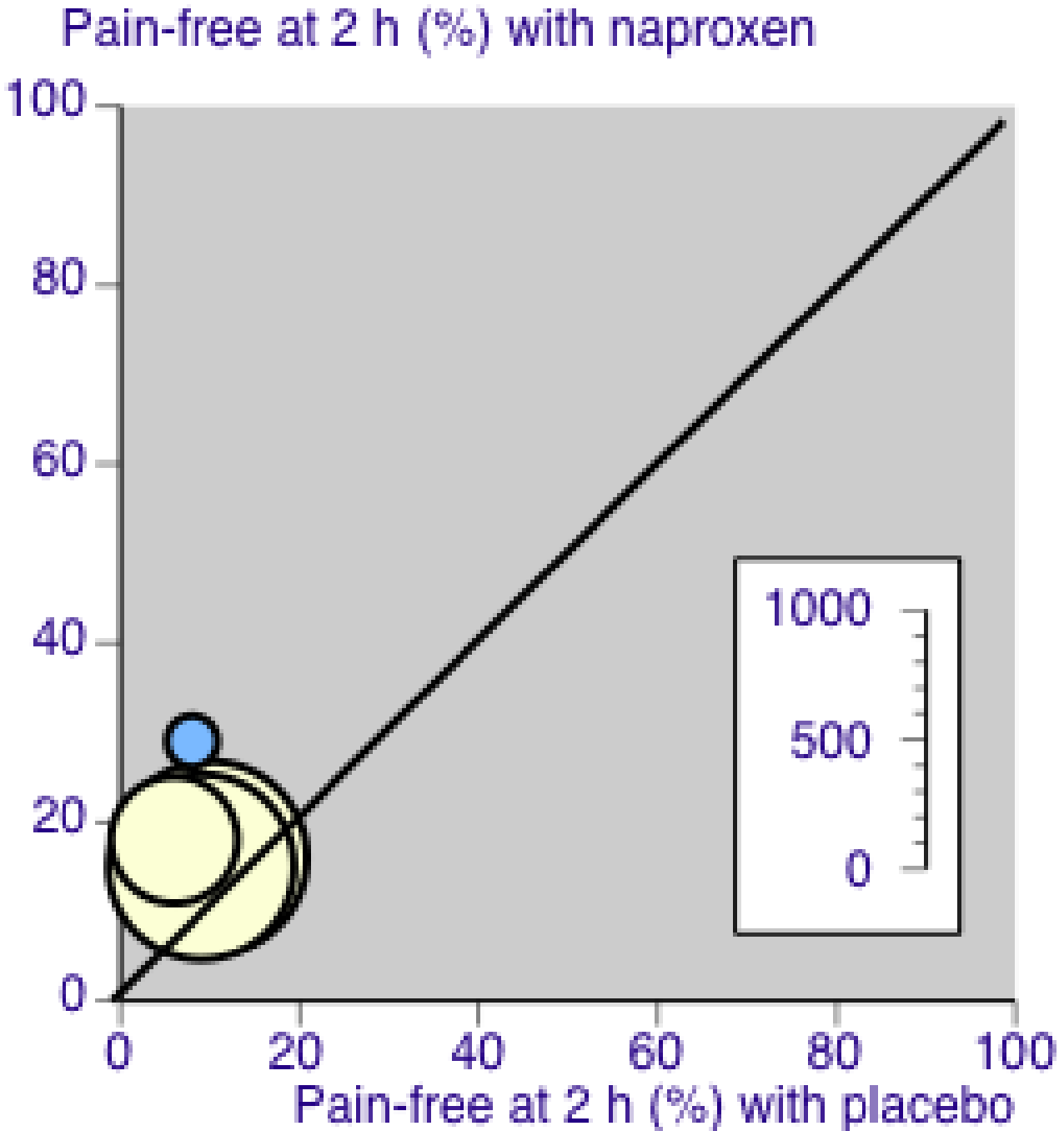
- The proportion of participants experiencing headache relief at two hours with naproxen 500/825 mg was 45% (482/1064; range 44% to 55%).
- The proportion of participants experiencing headache relief at two hours with placebo was 29% (311/1085; range 27% to 34%).

- The relative benefit of treatment compared with placebo was 1.6 (1.4 to 1.8) (Figure 5); the NNT was 6.0 (4.8 to 7.9).
- For naproxen 500 mg alone, the NNT was 6.2 (4.9 to 8.3), which was not significantly different from the NNT for the combined dosage.

Figure 5. Forest plot of comparison: 1 Pain, outcome: 1.4 Headache relief at two hours.

Study or Subgroup	Naproxen Events	Naproxen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Brandes 2007 Study 1	157	356	102	360	33.0%	1.56 [1.27 , 1.90]
Brandes 2007 Study 2	158	364	109	382	34.6%	1.52 [1.25 , 1.85]
Smith 2005	114	248	65	241	21.4%	1.70 [1.33 , 2.18]
Wentz 2008	53	96	35	102	11.0%	1.61 [1.16 , 2.22]
Total (95% CI)		**1064**		**1085**	**100.0%**	**1.58 [1.41 , 1.77]**
Total events:	482		311			

Heterogeneity: Chi² = 0.53, df = 3 (P = 0.91); I² = 0%
Test for overall effect: Z = 7.84 (P < 0.00001)
Test for subgroup differences: Not applicable

Favours placebo   Favours naproxen

The L'Abbé plot showed a considerable degree of similarity of response between different studies (Figure 6).

Figure 6. L'Abbé plot for headache relief at two hours. Size of circle proportional to size of study (see inset scale). Cream = naproxen 500 mg, blue = naproxen 825 mg.

Naproxen versus sumatriptan 50 mg

One study compared naproxen 500 mg with sumatriptan 50 mg (474 participants) (Smith 2005); 114/248 (46%) had PR at two hours with naproxen 500 mg compared with 111/226 (49%) with sumatriptan 50 mg. There were insufficient data for analysis.

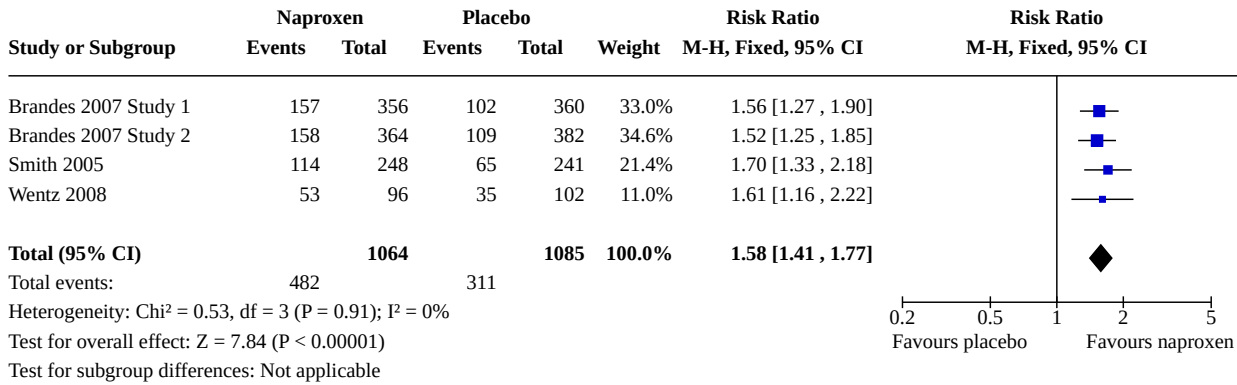### Sustained pain-free during the 24 hours post dose

Naproxen versus placebo

Four studies (2149 participants) provided data for use of naproxen, compared with placebo, when pain was moderate or severe (Brandes 2007 Study 1; Brandes 2007 Study 2; Smith 2005; Wentz 2008).
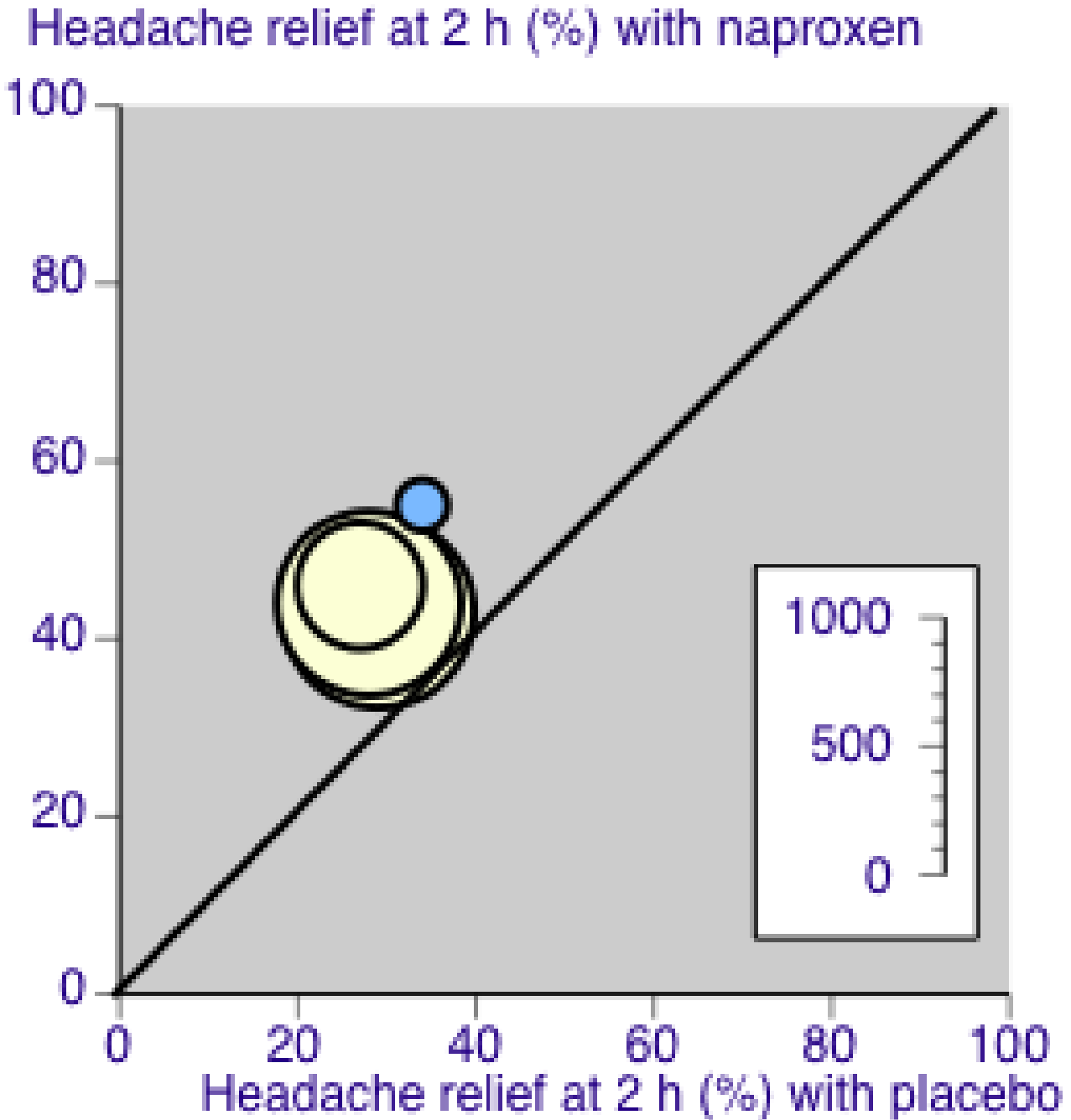
- The proportion of participants with a 24-hour sustained pain-free response with naproxen 500/825 mg was 12% (129/1064; range 10% to 26%).

- The proportion of participants with a 24-hour sustained pain-free response with placebo was 6.7% (73/1085; range 5.0% to 8.3%).
- The relative benefit of treatment compared with placebo was 1.8 (1.4 to 2.4) (Analysis 1.3); the NNT was 19 (13 to 34).
- For naproxen 500 mg alone, the NNT was 25 (16 to 70), which was not significantly different from the NNT for the combined dosage.

Naproxen versus sumatriptan 50 mg

One study compared naproxen 500 mg with sumatriptan 50 mg (474 participants) (Smith 2005); 30/248 (12%) had a sustained pain-free response during the 24 hours post dose with naproxen 500 mg compared with 25/226 (11%) with sumatriptan 50 mg. There were insufficient data for analysis.

Sustained headache relief during the 24 hours post dose

Naproxen versus placebo

Four studies (2149 participants) provided data for use of naproxen compared with placebo, when pain was moderate or severe (Brandes 2007 Study 1; Brandes 2007 Study 2; Smith 2005; Wentz 2008).

- The proportion of participants with 24-hour sustained headache relief with naproxen 500/825 mg was 30% (315/1064; range 25% to 46%);
- The proportion of participants with 24-hour sustained headache relief with placebo was 18% (190/1085; range 17% to 21%).
- The relative benefit of treatment compared with placebo was 1.7 (1.5 to 2.0) (Analysis 1.4); the NNT was 8.3 (6.4 to 12).
- For naproxen 500 mg alone, the NNT was 9.3 (6.9 to 14), which was not significantly different from the NNT for the combined dosage.

Naproxen versus sumatriptan 50 mg

One study (Smith 2005) compared naproxen 500 mg with sumatriptan 50 mg (474 participants); 62/248 (25%) had sustained headache relief during the 24 hours post dose with naproxen 500 mg compared with 66/226 (29%) with sumatriptan 50 mg. There were insufficient data for analysis.

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

Summary of results: Pain-free and headache relief

	Baseline pain	Studies	Attacks treated	Treatment (%)	Placebo or comparator (%)	Relative benefit (95% CI)	NNT (95% CI)
Pain-free at 2 h							
Naproxen 500/825 mg vs placebo	≥ mod	4	2149	17	8	2.0 (1.6 to 2.6)	11 (8.7 to 17)
Naproxen 500 mg vs placebo	≥ mod	3	1951	16	9	1.9 (1.5 to 2.4)	13 (9.7 to 22)
Naproxen 500 mg vs sumatriptan 50 mg	≥ mod	1	474	18	20	Not calculated	Not calculated
Headache relief at 2 h							
Naproxen 500/825 mg vs placebo	≥ mod	4	2149	45	29	1.6 (1.4 to 1.8)	6.0 (4.8 to 7.9)
Naproxen 500 mg vs placebo	≥ mod	3	1951	44	28	1.6 (1.4 to 1.8)	6.2 (4.9 to 8.3)
Naproxen 500 mg vs sumatriptan 50 mg	≥ mod	1	474	46	49	Not calculated	Not calculated
Sustained pain-free during the 24 h post dose							
Naproxen 500/825 mg vs placebo	≥ mod	4	2149	12	7	1.8 (1.4 to 2.4)	19 (13 to 34)
Naproxen 500 mg vs placebo	≥ mod	3	1951	11	7	1.6 (1.2 to 2.1)	26 (16 to 70)
Naproxen 500 mg vs sumatriptan 50 mg	≥ mod	1	474	12	11	Not calculated	Not calculated
Sustained headache relief during the 24 h post dose							
Naproxen 500/825 mg vs placebo	≥ mod	4	2149	30	18	1.7 (1.5 to 2.0)	8.3 (6.4 to 12)
Naproxen 500 mg vs placebo	≥ mod	3	1951	28	17	1.7 (1.4 to 2.0)	9.3 (6.9 to 14)
Naproxen 500 mg vs sumatriptan 50 mg	≥ mod	1	474	25	29	Not calculated	Not calculated

Subgroup analysis of primary outcomes

Subgroup analysis according to dose (500 mg versus 825 mg tablets) has been considered in the main analysis above. Inclusion of the higher dose did not significantly change the results. All studies used the oral route of administration, and none used multiple dosing strategies.

Sensitivity analysis of primary outcomes

All studies scored at least 3/5 for methodological quality on the Oxford Quality Scale, and no studies provided separate data for participants with or without aura, so no sensitivity analysis could be carried out for these criteria.

Adverse events

Any adverse event

All placebo-controlled studies reported some information about participants who experienced one or more adverse events, but the reporting was inconsistent. Brandes 2007 Study 1, Brandes 2007 Study 2 and Smith 2005 reported the number of participants in each treatment arm with at least one adverse event occurring within 24 hours of taking study medication, while Wentz 2008 reported numbers with adverse events until study discharge. Since there was no obvious relationship between numbers of participants with adverse events and the time over which the data were collected, we have combined data from the different time periods for analysis of the placebo-controlled studies.

Naproxen 500 mg to 825 mg versus placebo

Four studies (2174 participants) provided data for analysis (Brandes 2007 Study 1; Brandes 2007 Study 2; Smith 2005; Wentz 2008).

- The proportion of participants experiencing one or more adverse events with naproxen 500/825 mg was 15% (165/1078; range 13% to 17%).
- The proportion of participants experiencing one or more adverse events with placebo was 12% (128/1096; range 10% to 14%).
- The relative risk of treatment compared with placebo was 1.3 (1.1 to 1.6) (Analysis 1.5); the NNH was 28 (15 to 132).
- The relative risk of naproxen 500 mg compared with placebo was 1.2 (0.96 to 1.5); the NNH was not calculated.

There was no significant difference between naproxen 500 mg and placebo for participants with at least one adverse event.

Two studies comparing naproxen 275 mg with naratriptan 2.5 mg (S2WA4003; S2WA4004) provided data on the number of participants reporting any adverse event, but combined data for all attacks over 12 weeks of treatment without any explanation of how this was done, so we were unable to use them.

Specific adverse events

The most common specific adverse events reported in studies were dizziness, paraesthesia, somnolence, nausea, dyspepsia, dry mouth, and abdominal discomfort. The incidence of any specific event in individual studies was small (5% or less) and considered too low for useful analysis.

Serious adverse events

There were no reported serious adverse events related to study medication.

Withdrawals due to adverse events

Three placebo-controlled studies reported that there were no adverse event withdrawals due to naproxen (Brandes 2007 Study 1; Brandes 2007 Study 2; Wentz 2008), and another did not mention any adverse event withdrawals (Smith 2005). The active-controlled studies reported a total of 4/166 adverse event withdrawals with naproxen 275 mg and 3/173 with naratriptan 2.5 mg over the whole 12-week treatment period (S2WA4003; S2WA4004).

Exclusions of participants from analyses after randomisation were mostly due to protocol violations or failing to take the medication (no qualifying headache), or failure to document results in diary cards; they were generally well reported. Numbers of participants lost to follow-up, or withdrawing due for unspecified reasons were small and judged unlikely to influence results.

We classified participants who took rescue medication as withdrawals due to lack of efficacy, and details are reported under 'Use of rescue medication' (Appendix 7).

Other outcomes

Results for use of rescue medication, relief of headache-associated symptoms, and relief of functional disability are in Appendix 7.

D I S C U S S I O N

Summary of main results

This review included four randomised, double-blind, placebo-controlled studies using naproxen to treat a migraine attack when the pain was at least of moderate severity. For the primary outcome of pain-free at two hours, data were available for 1054 headaches treated with naproxen 500 mg or 825 mg and 1085 treated with placebo. Of these, 198 headaches were treated with naproxen 825 mg, and we analysed by both doses combined and by 500 mg alone.

For the IHS-preferred outcome of pain-free at two hours, naproxen was better than placebo when taken for moderate or severe PI; the NNT was 11 (8.7 to 17), with 17% and 8% of people being pain-free with naproxen and placebo, respectively. For headache relief at two hours, naproxen was better than placebo; the NNT was 6.0 (4.8 to 7.9), with 45% of participants responding compared with 29% with placebo. These results were obtained with 500 mg and 825 mg doses combined, but results were very similar with 500 mg alone.

Comparisons with other analgesics reviewed using identical methods show that naproxen was less effective than most other medicines available without prescription. For comparison, the NNT for two-hour pain-free response was 8.1 with aspirin 1000 mg (Kirthi 2013), 7.2 with ibuprofen 400 mg (Rabbie 2013), 12 with paracetamol 1000 mg (Derry 2013), and 6.1 with oral sumatriptan 50 mg (Derry 2012). The NNT for two-hour headache relief was 4.9 with aspirin 1000 mg (Kirthi 2013), 3.2 with ibuprofen 400 mg (Rabbie 2013), 5.0 with paracetamol 1000 mg (Derry 2013), and 4.0 with oral sumatriptan 50 mg (Derry 2012).

Results for sustained (24-hour) outcomes were modest, with NNTs of about 8 for 24-hour sustained headache relief, and 19 for 24-hour sustained pain-free.

Additional analyses show that naproxen was superior to placebo for use of rescue medication, and relief of migraine-associated symptoms (nausea, photophobia, and phonophobia) and functional disability, with NNTs of 6 to 10 (Appendix 7).

There was no significant difference in the number of participants experiencing one or more adverse events between naproxen 500 mg and placebo (RR 0.96 to 1.5). However, when the higher dose was included in the analysis there were slightly more adverse events than placebo (RR 1.1 to 1.6), giving an NNH of 28 (15 to 132). Most adverse events were described as mild or moderate, and transient. The incidence of any specific adverse event was low (5% or less), and no serious adverse events or adverse event withdrawals were reported.

Two active-controlled studies comparing a low dose (275 mg) of naproxen with a standard dose (2.5 mg) of naratriptan did not report any usable data (S2WA4003; S2WA4004).

Overall completeness and applicability of evidence

Included participants all had a diagnosis of migraine according to IHS criteria, and the information for comparators was sufficiently large to allow for comparisons with placebo in order to generate conclusions about relative efficacy and harm. Most participants were recruited from a pool of known headache sufferers, for example from neurology outpatient departments, and so may be more refractory to treatment than the general public as a whole, and were carefully screened and excluded if there was any contraindication to a study medication. These factors could lead to an underestimate of treatment effect, and overestimate of safety. All studies included participants with or without aura, but none reported results for the two types separately. Individual studies often are underpowered to determine differences between treatments for adverse events. Even pooling studies may not provide adequate numbers of events to demonstrate differences or allow confidence in the size of the effect. However, it is likely that adverse event data continued to be recorded after taking rescue medication, which may confound the results due to adverse events associated with the rescue medication itself. Single-dose studies are certainly unlikely to reveal rare, but potentially serious, adverse events; however, naproxen is a widely used NSAID, and rare, serious adverse events in occasional users for migraine are unlikely to differ in nature from, or be more frequent than, those in patients with conditions such as osteoarthritis who use naproxen regularly. Overall, in these studies, the number of participants experiencing any adverse event with active treatment was greater than with placebo.

We excluded six studies because they did not use IHS criteria to diagnose migraine (Andersson 1989; Johnson 1985; Nestvold 1985; Pradalier 1985; Sargent 1988; Treves 1992). A total of 462 participants were included in these studies, although not all provided evaluable data and not all received naproxen or placebo. None of the studies provided single-dose data, and none reported any of our primary outcomes.

We identified a small number of studies of a combination formulation of naproxen and metoclopramide (MT100: naproxen

sodium 500 mg plus metoclopramide 16 mg) manufactured by Pozen. We were unable to obtain any reports of the individual studies (despite contacting the manufacturer for full details of the trials); the drug did not receive a license from the US Food and Drug Administration (FDA) due to concerns about tardive dyskinesia associated with metoclopramide. For completeness we have included the results, such as they are available to us, in Appendix 8. We are also aware that there may be a combination formulation of naproxen and domperidone available in some parts of Asia (Martindale 2012), but have been unable to identify any studies.

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 (eg vomiting).

Potential biases in the review process

The main area of concern is the small numbers of events used to calculate some results, and particularly for specific adverse events, where no analysis was possible. We identified a large amount of data in comparisons with placebo. The NNTs for two-hour pain-free and two-hour headache relief, at 8 and 6, respectively, were already at the preset limits for determining clinical utility, and so the calculation of how much additional data with null effect would be required to reach that point could not be done (Moore 2008). However, a simple calculation showed that even the addition of three times the available data in unpublished trials with null effect would still produce a statistically significant benefit, even if clinically unimportant. It is unlikely that such a large amount of unidentified data exists, so publication bias overturning the direction of the result (that naproxen is statistically better than placebo) is not a concern.

Agreements and disagreements with other studies or reviews

A systematic review of naproxen alone for acute migraine was carried out in Bandolier, identifying five studies up to June 2000 (Bandolier 2000). Only 225 participants were treated with naproxen and 190 with placebo, and most studies were small, predating IHS criteria for diagnosis and IHS-preferred outcomes; none of those studies is included in this review because of the absence of IHS diagnosis of migraine. Only one study reported the outcome of headache relief at two hours (Andersson 1989). Naproxen at doses ranging from 750 mg/day to 1250 mg/day provided significantly better PR than placebo in the four placebo-controlled studies, while the two studies comparing it with ergotamine 2 mg to 3 mg showed no significant difference between the two drugs.

Suthisisang 2010 is a meta-analysis of the four included studies in this review that contributed to analyses (Brandes 2007 Study 1; Brandes 2007 Study 2; Smith 2005; Wentz 2008). The meta-analysis quotes NNT values for naproxen versus placebo of 10 (7 to 25) for pain-free at two hours, 15 (9 to 100) for sustained pain-free during the 24 hours post dose, 7 (5 to 9) for headache relief at two hours, and 9 (7 to 13) for sustained headache relief during the

24 hours post dose. These results are consistent with the results reported in this review for the same comparison with the same studies; minor differences appear to arise from the use of slightly different denominators in the analyses, and do not substantially affect the results. The authors concur that naproxen is unlikely to be considered as a first-line therapy, given the superiority of other simple analgesics (aspirin and ibuprofen) for important outcomes such as pain-free at two hours.

Another review of NSAID treatments for migraine was neither systematic nor did it provide any analysis (Pardutz 2010).

AUTHORS' CONCLUSIONS

Implications for practice

This review suggests that naproxen is effective in migraine headache for a small proportion of sufferers. Other Cochrane reviews examining alternative monotherapies, such as aspirin, ibuprofen, paracetamol, or sumatriptan have reported better (lower) NNT results for the same outcome, so are effective in more people.

Implications for research

Analgesics effective in acute and chronic painful conditions typically have a much lesser effect in migraine. This is especially the case when using the IHS criterion of pain-free at two hours as the outcome. Naproxen is no exception when used alone, and the combination with sumatriptan has been evaluated in clinical trials and a Cochrane review (Law 2013). In these circumstances, no further research with naproxen for migraine is warranted.

ACKNOWLEDGEMENTS

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Brandes 2007 Study 1 *{published data only}*

* Brandes JL, Kudrow D, Stark SR, O'Carroll CP, Adelman JU, O'Donnell FJ, et al. Sumatriptan-naproxen for acute treatment of migraine: a randomized trial. *JAMA* 2007;**297**(13):1443-54. [DOI: 10.1001/jama.297.13.1443]

Landy S, DeRossett SE, Rapoport A, Rothrock J, Ames MH, McDonald SA, et al. Two double-blind, multicenter, randomized, placebo-controlled, single-dose studies of sumatriptan/ naproxen sodium in the acute treatment of migraine: function, productivity, and satisfaction outcomes. *Medscape General Medicine* 2007;**9**(2):53.

Brandes 2007 Study 2 *{published data only}*

* Brandes JL, Kudrow D, Stark SR, O'Carroll CP, Adelman JU, O'Donnell FJ, et al. Sumatriptan-naproxen for acute treatment of migraine: a randomized trial. *JAMA* 2007;**297**(13):1443-54. [DOI: 10.1001/jama.297.13.1443]

Landy S, DeRossett SE, Rapoport A, Rothrock J, Ames MH, McDonald SA, et al. Two double-blind, multicenter, randomized, placebo-controlled, single-dose studies of sumatriptan/ naproxen sodium in the acute treatment of migraine: function, productivity, and satisfaction outcomes. *Medscape General Medicine* 2007;**9**(2):53.

S2WA4003 *{published data only}*

Anonymous. A randomized, double-blind, double-dummy, active-placebo controlled, parallel group evaluation of oral naratriptan (2.5mg) compared to oral naproxen sodium (275mg) on migraine-related quality of life. Result summary for S2WA4003. download.gsk-clinicalstudyregister.com/ files/2014.pdf (accessed 19 September 2013).

S2WA4004 *{published data only}*

Anonymous. A randomized, double-blind, double-dummy, active-placebo controlled, parallel group evaluation of oral naratriptan (2.5mg) compared to oral naproxen sodium (275mg) on migraine-related quality of life. Result summary for S2WA4004. download.gsk-clinicalstudyregister.com/ files/2041.pdf (accessed 19 September 2013).

Smith 2005 *{published data only}*

Smith TR, Sunshine A, Stark SR, Littlefield DE, Spruill SE, Alexander WJ. Sumatriptan and naproxen sodium for the acute treatment of migraine. *Headache* 2005;**45**(8):983-91. [DOI: 10.1111/j.1526-4610.2005.05178.x]

Wentz 2008 *{published data only}*

Wentz AL, Jimenez TB, Dixon RM, Aurora SK, Gold M, CXA20008 Study Investigators. A double-blind, randomized, placebo-controlled, single-dose study of thecyclooxygenase-2 inhibitor, GW406381, as a treatment for acute migraine. *European Journal of Neurology* 2008;**15**(4):420-7. [DOI: 10.1111/ j.1468-1331.2008.02093.x]

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Brandes 2007 Study 1

Study characteristics

Methods	Multicentre, R, DB, PC, parallel-group. Single dose to treat a single attack Medication taken when PI ≥ moderate Assessments at 0, 0.5, 1, 1.5, 2, then hourly to 24 h
Participants	Migraine ± aura (IHS 2004), aged 18-65 years. History: > 6 months with frequency of 2-6 per month and untreated severity ≥ moderate Excluded: uncontrolled hypertension, cardio- or cerebrovascular disease, using MAOI, ergot, SJW, or NSAID N = 1461 F = 86% Mean age 40 years 72% without aura
Interventions	Sumatriptan 85 mg/naproxen 500 mg, n = 370 (364 analysed for efficacy) Sumatriptan 85 mg, n = 365 (361 for efficacy) Naproxen 500 mg, n = 361 (365 for efficacy) Placebo, n = 365 (360 for efficacy) Rescue medication allowed after 2 h if necessary (as prescribed by physician but not ergot-containing, serotonin agonist, or NSAID-containing medications)
Outcomes	Headache relief at 2 h Pain-free at 2 h 24-h sustained headache relief 24-h sustained pain-free Presence and relief of associated symptoms at 2 h Presence and relief of functional disability at 2 h (from Landy 2007) Use of rescue medication Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB1, W1. Total = 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs described

Brandes 2007 Study 1 *(Continued)*

Size	Low risk	> 200 participants in each treatment arm

Brandes 2007 Study 2

Study characteristics

Methods	Multicentre, R, DB, PC, parallel-group. Single dose to treat a single attack Medication taken when PI ≥ moderate Assessments at 0, 0.5, 1, 1.5, 2, then hourly to 24 h
Participants	Migraine ± aura (IHS 2004), aged 18-65 years. History: > 6 months with frequency of 2-6 per month and untreated severity ≥ moderate Excluded: uncontrolled hypertension, cardio- or cerebrovascular disease, using MAOI, ergot, SJW, or NSAID N = 1495 F = 88% Mean age 40 years 76% without aura
Interventions	Sumatriptan 85 mg/naproxen 500 mg, n = 367 (362 for efficacy) Sumatriptan 85 mg, n = 370 (362 for efficacy) Naproxen 500 mg, n = 371 (364 for efficacy) Placebo, n = 387 (382 for efficacy) Rescue medication allowed after 2 h if necessary (as prescribed by physician but not ergot-containing, serotonin agonist, or NSAID-containing medications)
Outcomes	Headache relief at 2 h Pain-free at 2 h 24-h sustained headache relief 24-h sustained pain-free Presence and relief of associated symptoms at 2 h Presence and relief of functional disability at 2 h (from Landy 2007) Use of rescue medication Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB1, W1. Total = 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias)	Unclear risk	Not described

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Brandes 2007 Study 2 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs described
Size	Low risk	> 200 participants in each treatment arm

S2WA4003

Study characteristics

Methods	Multicentre, R, DB, PC, parallel-group. Single dose to treat single attack; several attacks treated over 12 weeks
	Medication taken when PI ≥ moderate
	Assessments at 0, 4 h, for efficacy and adverse events, MSQ at baseline and after 12 weeks of treatment
Participants	Migraine ± aura (IHS 1988), aged 18-65 years. History: > 12 months with frequency of 1-6 per month and untreated severity ≥ moderate
	Excluded: previous use of triptan on > 3 occasions or had prescription for sumatriptan, ischaemic disease or symptoms, cardio- or cerebrovascular pathology, uncontrolled hypertension, epilepsy
	N = 168 F = 85% Mean age 39 years
Interventions	Naproxen sodium 275 mg, n = 81
	Naratriptan 2.5 mg, n = 87
Outcomes	Adverse events
	Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double dummy" method
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Double dummy" method

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S2WA4003 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for
Size	Unclear risk	50-200 participants in each treatment arm

S2WA4004

Study characteristics

Methods	Multicentre, R, DB, PC, parallel-group. Single dose to treat single attack; several attacks treated over 12 weeks Medication taken when PI ≥ moderate Assessments at 0, 4 h, for efficacy and adverse events, MSQ at baseline and after 12 weeks of treatment
Participants	Migraine ± aura (IHS 1988), aged 18-65 years. History: > 12 months with frequency of 1-6 per month and untreated severity ≥ moderate Excluded: previous use of triptan on > 3 occasions or had prescription for sumatriptan, ischaemic disease or symptoms, cardio- or cerebrovascular pathology, uncontrolled hypertension, epilepsy N = 171 F = 85% Mean age 37 years
Interventions	Naproxen sodium 275 mg, n = 85 Naratriptan 2.5 mg, n = 86
Outcomes	Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double dummy" method
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Double dummy" method
Incomplete outcome data (attrition bias)	Low risk	All participants accounted for

All outcomes

Size	Unclear risk	50-200 participants in each treatment arm

Smith 2005

Study characteristics

Methods	Multicentre, R, DB, DD, parallel-group. Single dose to treat a single attack Medication taken when pain ≥ moderate Assessments at 0, 15 min intervals to 2 h, 30 min to 4 h, hourly to 24 h
Participants	Migraine ± aura (IHS 2004), aged ≥ 18 years. History ≥ 1 year with 2-6 attacks per month, and able to tolerate oral triptan or ergot derivative N = 972 F = 91% Mean age 42 years Without aura: > 70%
Interventions	Sumatriptan 50 mg + naproxen 500 mg, n = 251 Sumatriptan 50 mg, n = 229 Naproxen 500 mg, n = 250 Placebo, n = 242 Rescue medication allowed after 2 h if necessary (not specified)
Outcomes	Headache relief at 1 and 2 h Pain-free at 2 h 24-h sustained headache relief 24-h sustained pain-free Presence and relief of functional disability at 2 h Presence and relief of associated symptoms at 2 h Use of rescue medication Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy method
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-dummy method

Smith 2005 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs described
Size	Low risk	> 200 participants in each treatment arm

Wentz 2008

Study characteristics

Methods	Multicentre, multinational, R, DB, PC, parallel-group, double-dummy study. Single dose to treat a single attack
	Medication taken when PI ≥ moderate
	Assessments at 0, 0.5, 1, 1.5, 2, 3, 4 h
Participants	Migraine ± aura (IHS 2004), aged 18-65 years. History > 6 months Frequency 6/month with untreated severity ≥ moderate Excluded if > 15 headache days/month, associated disease, or if on acute or prophylactic medication
	N = 284 (safety population, 283 for efficacy)
	F = 81%
	Mean age 41 years
	Without aura: > 80%
Interventions	Naproxen 825 mg, n = 109
	Placebo, n = 117
	Rescue medication allowed after 2 h (patient's usual medication)
	111 participants were also treated with an experimental COX-2 inhibitor (GW406381), which is not marketed
Outcomes	Headache relief at 1, 2, and 4 h
	Pain-free response at 1 and 2 h
	24-h sustained headache relief
	24-h sustained pain-free
	Adverse events
	Withdrawals
	Presence and relief of headache associated symptoms at 2 hours
	Use of rescue medication
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5

Risk of bias

Bias	Authors' judgement	Support for judgement

Wentz 2008 *(Continued)*

Random sequence generation (selection bias)	Low risk	Randomised by computer-generated sequence
Allocation concealment (selection bias)	Low risk	No concealment of allocations prior to assignments
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy blinding method used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-dummy blinding method used
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs accounted for
Size	Unclear risk	50-200 participants in each treatment arm

COX: cyclooxygenase; DB: double-blind; IHS: International Headache Society; MAOI: monoamine oxidase inhibitor; MSQ: Migraine-Specific Quality of Life Questionnaire; N: number of participants in study; n: number of participants in treatment arm; NSAID: non-steroidal anti-inflammatory drug; PC: placebo-controlled; PI: pain intensity; R: randomised; SJW: St John's Wort; W: withdrawals.

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

Study	Reason for exclusion
Adis 2006	Not RCT - general review of naproxen sodium/metoclopramide formulation from Pozen Inc. Data from the Pozen studies are included in Appendix 8
Andersson 1989	Did not use IHS diagnostic criteria (or equivalent) for migraine - diagnostic criteria judged not equivalent to IHS criteria
Johnson 1985	Did not use IHS diagnostic criteria (or equivalent) for migraine - no diagnostic criteria reported
Krymchantowski 2005	Not randomised. Quasi-randomised only
Misra 2010	Fewer than 10 participants/treatment arm
NCT01726920	Not double blind
Nestvold 1985	Did not use IHS diagnostic criteria (or equivalent) for migraine - diagnostic criteria judged not equivalent to IHS criteria
Nestvold 1986	Supplement article, not original study report (same study as Nestvold 1985), no additional data
Pradalier 1985	Did not use IHS diagnostic criteria (or equivalent) for migraine - diagnostic criteria judged not equivalent to IHS criteria
Sargent 1988	Did not use IHS diagnostic criteria (or equivalent) for migraine - diagnostic criteria judged not equivalent to IHS criteria
Smith 2007	Same study as Smith 2005, but reporting only quality-of-life and satisfaction outcomes

Study	Reason for exclusion
Stronks 2003	Low patient numbers (12 only). No data on individual attacks. A comparative study versus naratriptan without placebo
Treves 1992	Did not use IHS diagnostic criteria (or equivalent) for migraine - diagnostic criteria judged not equivalent to IHS criteria
Welch 1986	Supplement article, not original study report

IHS: International Headache Society; RCT: randomised controlled trial.

Characteristics of studies awaiting classification [ordered by study ID]

NCT01390324

Methods	Multicentre, randomised, double-blind, parallel-group
Participants	Migraine ± aura (IHS 2004 criteria), male or female, 3-month history of 2-6 moderate/severe attacks per month, aged 18-65 years
Interventions	Naratriptan 2.5 mg + naproxen 500 mg
	Naratriptan 2.5 mg
	Naproxen 500 mg
Outcomes	Headache relief at 2 and 4 h
	Pain-free at 2 and 4 h
	24-h sustained headache relief
	24-h sustained pain-free
	Associated symptoms
	Use of rescue medication
	Adverse events
Notes	Scheduled primary completion date October 2012
	Contact person asked for update January 2013

IHS: International Headache Society.

DATA AND ANALYSES

Comparison 1.   Naproxen versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Pain-free response at 2 h	4	2149	Risk Ratio (M-H, Fixed, 95% CI)	2.03 [1.61, 2.58]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 Headache relief at 2 h	4	2149	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [1.41, 1.77]
1.3 24-h sustained pain-free	4	2149	Risk Ratio (M-H, Fixed, 95% CI)	1.81 [1.37, 2.38]
1.4 24-h sustained headache relief	4	2149	Risk Ratio (M-H, Fixed, 95% CI)	1.69 [1.45, 1.98]
1.5 Any adverse event	4	2174	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [1.05, 1.62]
1.6 Use of rescue medication	4	2149	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.65, 0.78]
1.7 Relief of associated symptoms	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.7.1 Nausea	3	782	Risk Ratio (M-H, Fixed, 95% CI)	1.73 [1.38, 2.16]
1.7.2 Photophobia	3	1342	Risk Ratio (M-H, Fixed, 95% CI)	1.73 [1.43, 2.10]
1.7.3 Phonophobia	3	1313	Risk Ratio (M-H, Fixed, 95% CI)	1.68 [1.40, 2.01]
1.8 Relief of functional disability	2	1346	Risk Ratio (M-H, Fixed, 95% CI)	2.14 [1.62, 2.84]

Analysis 1.1. Comparison 1: Naproxen versus placebo, Outcome 1: Pain-free response at 2 h

Study or Subgroup	Naproxen Events	Naproxen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Brandes 2007 Study 1	53	356	33	360	36.1%	1.62 [1.08 , 2.45]	
Brandes 2007 Study 2	57	364	37	382	39.7%	1.62 [1.10 , 2.38]	
Smith 2005	45	248	14	241	15.6%	3.12 [1.76 , 5.54]	
Wentz 2008	28	96	8	102	8.5%	3.72 [1.78 , 7.75]	
Total (95% CI)		1064		1085	100.0%	**2.03 [1.61 , 2.58]**	
Total events:	183		92				

Heterogeneity: Chi² = 7.25, df = 3 (P = 0.06); I² = 59%
Test for overall effect: Z = 5.89 (P < 0.00001)
Test for subgroup differences: Not applicable

0.2   0.5   1   2   5
Favours placebo   Favours naproxen

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Analysis 1.2. Comparison 1: Naproxen versus placebo, Outcome 2: Headache relief at 2 h

Study or Subgroup	Naproxen		Placebo			Risk Ratio	Risk Ratio
	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Brandes 2007 Study 1	157	356	102	360	33.0%	1.56 [1.27 , 1.90]	
Brandes 2007 Study 2	158	364	109	382	34.6%	1.52 [1.25 , 1.85]	
Smith 2005	114	248	65	241	21.4%	1.70 [1.33 , 2.18]	
Wentz 2008	53	96	35	102	11.0%	1.61 [1.16 , 2.22]	
Total (95% CI)		**1064**		**1085**	**100.0%**	**1.58 [1.41 , 1.77]**	
Total events:	482		311				

Heterogeneity: Chi² = 0.53, df = 3 (P = 0.91); I² = 0%
Test for overall effect: Z = 7.84 (P < 0.00001)
Test for subgroup differences: Not applicable

0.2　0.5　1　2　5
Favours placebo　Favours naproxen

Analysis 1.3. Comparison 1: Naproxen versus placebo, Outcome 3: 24-h sustained pain-free

Study or Subgroup	Naproxen		Placebo			Risk Ratio	Risk Ratio
	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Brandes 2007 Study 1	37	356	30	360	41.3%	1.25 [0.79 , 1.97]	
Brandes 2007 Study 2	37	364	25	382	33.8%	1.55 [0.95 , 2.53]	
Smith 2005	30	248	12	241	16.9%	2.43 [1.27 , 4.63]	
Wentz 2008	25	96	6	102	8.1%	4.43 [1.90 , 10.32]	
Total (95% CI)		**1064**		**1085**	**100.0%**	**1.81 [1.37 , 2.38]**	
Total events:	129		73				

Heterogeneity: Chi² = 7.99, df = 3 (P = 0.05); I² = 62%
Test for overall effect: Z = 4.22 (P < 0.0001)
Test for subgroup differences: Not applicable

0.2　0.5　1　2　5
Favours placebo　Favours naproxen

Analysis 1.4. Comparison 1: Naproxen versus placebo, Outcome 4: 24-h sustained headache relief

Study or Subgroup	Naproxen		Placebo			Risk Ratio	Risk Ratio
	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Brandes 2007 Study 1	107	356	64	360	33.8%	1.69 [1.29 , 2.22]	
Brandes 2007 Study 2	102	364	64	382	33.2%	1.67 [1.27 , 2.21]	
Smith 2005	62	248	41	241	22.1%	1.47 [1.03 , 2.09]	
Wentz 2008	44	96	21	102	10.8%	2.23 [1.44 , 3.45]	
Total (95% CI)		**1064**		**1085**	**100.0%**	**1.69 [1.45 , 1.98]**	
Total events:	315		190				

Heterogeneity: Chi² = 2.12, df = 3 (P = 0.55); I² = 0%
Test for overall effect: Z = 6.51 (P < 0.00001)
Test for subgroup differences: Not applicable

0.2　0.5　1　2　5
Favours placebo　Favours naproxen

Analysis 1.5. Comparison 1: Naproxen versus placebo, Outcome 5: Any adverse event

Study or Subgroup	Naproxen Events	Naproxen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Brandes 2007 Study 1	48	361	45	365	35.2%	1.08 [0.74 , 1.58]	
Brandes 2007 Study 2	52	371	39	387	30.0%	1.39 [0.94 , 2.05]	
Smith 2005	43	250	36	242	28.7%	1.16 [0.77 , 1.74]	
Wentz 2008	22	96	8	102	6.1%	2.92 [1.37 , 6.25]	
Total (95% CI)		**1078**		**1096**	**100.0%**	**1.31 [1.05 , 1.62]**	
Total events:	165		128				

Heterogeneity: Chi² = 5.74, df = 3 (P = 0.13); I² = 48%

Test for overall effect: Z = 2.44 (P = 0.01)

Test for subgroup differences: Not applicable

0.2 0.5 1 2 5
Favours naproxen   Favours placebo

Analysis 1.6. Comparison 1: Naproxen versus placebo, Outcome 6: Use of rescue medication

Study or Subgroup	Naproxen Events	Naproxen Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Brandes 2007 Study 1	135	356	192	360	30.6%	0.71 [0.60 , 0.84]	
Brandes 2007 Study 2	143	364	223	382	34.9%	0.67 [0.58 , 0.78]	
Smith 2005	129	248	154	241	25.0%	0.81 [0.70 , 0.95]	
Wentz 2008	33	96	61	102	9.5%	0.57 [0.42 , 0.79]	
Total (95% CI)		**1064**		**1085**	**100.0%**	**0.71 [0.65 , 0.78]**	
Total events:	440		630				

Heterogeneity: Chi² = 5.23, df = 3 (P = 0.16); I² = 43%

Test for overall effect: Z = 7.66 (P < 0.00001)
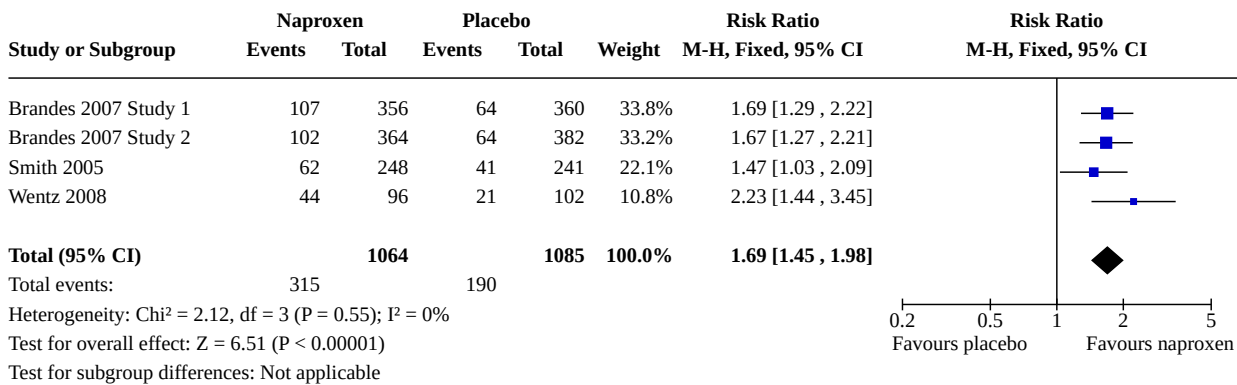
Test for subgroup differences: Not applicable

0.2 0.5 1 2 5
Favours naproxen   Favours placebo

Analysis 1.7. Comparison 1: Naproxen versus placebo, Outcome 7: Relief of associated symptoms

| Study or Subgroup | Naproxen | | Placebo | | Weight | Risk Ratio | Risk Ratio |
	Events	Total	Events	Total		M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
1.7.1 Nausea							
Brandes 2007 Study 1	66	174	22	149	26.9%	2.57 [1.67 , 3.95]	
Brandes 2007 Study 2	60	175	50	188	54.6%	1.29 [0.94 , 1.76]	
Wentz 2008	30	49	16	47	18.5%	1.80 [1.14 , 2.84]	
Subtotal (95% CI)		**398**		**384**	**100.0%**	**1.73 [1.38 , 2.16]**	
Total events:	156		88				
Heterogeneity: Chi² = 6.64, df = 2 (P = 0.04); I² = 70%							
Test for overall effect: Z = 4.83 (P < 0.00001)							
1.7.2 Photophobia							
Brandes 2007 Study 1	97	287	57	286	45.6%	1.70 [1.28 , 2.25]	
Brandes 2007 Study 2	85	301	50	310	39.4%	1.75 [1.28 , 2.39]	
Wentz 2008	33	78	19	80	15.0%	1.78 [1.11 , 2.85]	
Subtotal (95% CI)		**666**		**676**	**100.0%**	**1.73 [1.43 , 2.10]**	
Total events:	215		126				
Heterogeneity: Chi² = 0.04, df = 2 (P = 0.98); I² = 0%							
Test for overall effect: Z = 5.61 (P < 0.00001)							
1.7.3 Phonophobia							
Brandes 2007 Study 1	90	265	56	278	40.3%	1.69 [1.26 , 2.25]	
Brandes 2007 Study 2	91	296	62	316	44.2%	1.57 [1.18 , 2.08]	
Wentz 2008	40	76	22	82	15.6%	1.96 [1.29 , 2.97]	
Subtotal (95% CI)		**637**		**676**	**100.0%**	**1.68 [1.40 , 2.01]**	
Total events:	221		140				
Heterogeneity: Chi² = 0.77, df = 2 (P = 0.68); I² = 0%							
Test for overall effect: Z = 5.59 (P < 0.00001)							

Test for subgroup differences: Chi² = 0.07, df = 2 (P = 0.97), I² = 0%

0.2 0.5 1 2 5
Favours placebo   Favours naproxen

Analysis 1.8. Comparison 1: Naproxen versus placebo, Outcome 8: Relief of functional disability

| Study or Subgroup | Naproxen | | Placebo | | Weight | Risk Ratio | Risk Ratio |
	Events	Total	Events	Total		M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Brandes 2007 Study 1	71	331	36	328	58.7%	1.95 [1.35 , 2.83]	
Brandes 2007 Study 2	60	336	26	351	41.3%	2.41 [1.56 , 3.73]	
Total (95% CI)		**667**		**679**	**100.0%**	**2.14 [1.62 , 2.84]**	
Total events:	131		62				
Heterogeneity: Chi² = 0.52, df = 1 (P = 0.47); I² = 0%							
Test for overall effect: Z = 5.30 (P < 0.00001)							
Test for subgroup differences: Not applicable							

0.2 0.5 1 2 5
Favours placebo   Favours naproxen

A P P E N D I C E S

Appendix 1. Definitions

All terms relating to primary efficacy outcomes are defined according to the effect of the treatment on headache pain, measured using a 4-point pain intensity (PI) scale (ranging from 0 to 3 or none, mild, moderate, and severe).

- Baseline PI - level of pain participant must be experiencing in order to receive study medication, either 1 (mild pain) or 2/3 (moderate or severe pain).
- Pain-free at two hours - number of participants with a PI of 0 (none) at two hours after administration of study medication, expressed as a fraction of the treated participants with the appropriate baseline pain.
- Pain-free at one hour - number of participants with a PI of 0 (none) at one hour after administration of study medication, expressed as a fraction of the treated participants with the appropriate baseline pain.
- Headache relief at two hours - number of participants with a reduction in PI from 2/3 (moderate/severe) to 0/1 (none/mild) at two hours after administration of study medication, expressed as a fraction of the treated participants with grade 2/3 baseline pain.
- Headache relief at one hour - number of participants with a reduction in PI from 2/3 (moderate/severe) to 0/1 (none/mild) at one hour after administration of study medication, expressed as a fraction of the treated participants with grade 2/3 baseline pain.
- 24-hour sustained headache relief - number of participants with a reduction in PI from 2/3 (moderate/severe) to 0/1 (none/mild) at two hours after administration of study medication which is then sustained between 2 and 24 hours without recurrence of headache or use of additional medication, expressed as a fraction of the treated participants with grade 2/3 baseline pain.
- 24-hour sustained pain-free - number of participants with a PI of 0 (none) at two hours after administration of study medication which is then sustained between 2 and 24 hours without recurrence of headache or use of additional medication expressed as a fraction of the treated participants with the appropriate baseline pain.
- Use of rescue medication - number of participants requiring the use of additional medication to treat an inadequate response to study medication, provided that the additional medication is not, or does not include, the study drug.
- Relief of associated symptoms - number of participants with an absence of a headache-associated symptom (nausea, vomiting, photophobia, or phonophobia) at two hours after administration of study medication, expressed as a fraction of the treated participants for whom the symptom was present at baseline.
- Complete relief of functional disability - reduction in the level of functional disability, measured using a 4-point scale, from any degree of disability (grade 1/2/3) at baseline to grade 0 (able to work/function normally) at two hours after administration of study medication, expressed as a fraction of the treated participants with any functional disability at baseline.

Appendix 2. Search strategy for CENTRAL

1. MeSH descriptor Naproxen
2. (naproxen or Aleve or Anaprox or Antalgin or Feminax or Flanax or Inza or Midol or Miranax or Nalgesin or Naposin or Naprelan or Naprogesic or Naprosyn or Narocin or Proxen or Synflex or Xenobid):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 3. Search strategy for MEDLINE (via Ovid)

1. Naproxen/
2. (naproxen or Aleve or Anaprox or Antalgin or Feminax or Flanax or Inza or Midol or Miranax or Nalgesin or Naposin or Naprelan or Naprogesic or Naprosyn or Narocin or Proxen or Synflex or Xenobid).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 4. Search strategy for EMBASE (via Ovid)

1. Naproxen/

2. (naproxen or Aleve or Anaprox or Antalgin or Feminax or Flanax or Inza or Midol or Miranax or Nalgesin or Naposin or Naprelan or Naprogesic or Naprosyn or Narocin or Proxen or Synflex or Xenobid).mp

3. 1 OR 2

4. Headache/ OR exp Headache and facial pain/

5. exp Migraine/

6. (headach* OR migrain* OR cephalgi* OR cephalalgi*).mp.

7. 4 OR 5 OR 6

8. clinical trials.sh.

9. controlled clinical trials.sh.

10.randomized controlled trial.sh.

11.double-blind procedure.sh.

12.(clin* adj25 trial*).ab.

13.((doubl* or trebl* or tripl*) adj25 (blind* or mask*)).ab.

14.placebo*.ab.

15.random*.ab.

16.OR/8-15

17.3 AND 7 AND 16

Study ID	Treatment	HR 1 h	HR 2 h	PF 2 h	SHR 24 h	SPF 24 h	Use of rescue medication
Brandes 2007 Study 1	(1) naprox 500 mg, n = 361 (2) placebo, n = 365	No data	(1) 157/356 (2) 102/360	(1) 53/356 (2) 33/360	(1) 107/365 (2) 64/360	(1) 37/356 (2) 30/360	From 2 to 24 h (1) 135/356 (2) 192/360
Brandes 2007 Study 2	(1) naprox 500 mg, n = 371 (2) placebo, n = 387	No data	(1) 158/364 (2) 109/382	(1) 57/364 (2) 37/382	(1) 102/364 (2) 64/382	(1) 37/364 (2) 25/382	From 2 to 24 h (1) 143/364 (2) 223/382
Smith 2005	(1) naprox 500 mg, n = 250 (2) placebo, n = 241	(1) 67/248 (2) 29/241	(1) 114/248 (2) 65/241	(1) 45/248 (2) 14/241	(1) 62/248 (2) 41/241	(1) 30/248 (2) 12/241	From 2 to 24 h (1) 129/248 (2) 154/241
Wentz 2008	(1) naprox 825 mg, n = 96 (2) placebo, n = 102	(1) 32/96 (2) 12/102	(1) 53/96 (2) 35/102	(1) 28/96 (2) 8/102	(1) 44/96 (2) 21/102	(1) 25/96 (2) 6/102	(1) 33/96 (2) 61/102

HR: headache relief; naprox: naproxen; PF: pain-free; SHR: sustained headache relief; SPF: sustained pain free.

Appendix 6. Results for individual studies: adverse events and withdrawals in placebo-controlled studies

Study ID	Treatment	Any AE	SAE	AE withdrawal	Other withdrawal
Brandes 2007 Study 1	(1) naprox 500 mg, n = 361 (2) placebo, n = 365	≤ 24 h: (1) 48/361 (2) 45/365	No SAE reported	None reported	Exclusions - took medication but no evaluable data: (1) 5 (2) 5
Brandes 2007 Study 2	(1) naprox 500 mg, n = 371 (2) placebo, n = 387	≤ 24 h: (1) 52/371 (2) 39/387	No SAE reported	None reported	Exclusions - took medication but no evaluable data: (1) 7 (2) 5
Smith 2005	(1) naprox 500 mg, n = 250 (2) placebo, n = 241	AE reported for safety population at 72 h (1) 55/250 (2) 36/242	None	None	None reported
Wentz 2008	(1) naprox 825 mg, n = 96 (2) placebo, n = 102	AE reported until 'study discharge' (1) 22/96 (2) 8/102	None	None	16 excluded (10 had no qualifying headache, 3 lost to follow-up, 1 protocol violation, 2 'other')

AE: adverse event; naprox: naproxen; SAE: serious adverse event.

Appendix 7. Other outcomes

Use of rescue medication

All studies asked participants whose symptoms were not adequately controlled to wait for two hours before taking any additional medication in order to give the test medication enough time to have an effect. Use of rescue or 'escape' medication (usually a different analgesic) after that time was reported in all studies and is a measure of treatment failure (lack of efficacy). The time over which use of rescue medication was measured was 24 hours.

All four studies (2149 participants) provided data for naproxen compared with placebo, when pain was moderate or severe; 41% of participants needed rescue medication with naproxen 500/825 mg, and 58% with placebo. The relative benefit was 0.71 (0.65 to 0.78) (Analysis 1.6) and the NNTp was 6.0 (4.8 to 8.0). For 500 mg alone, the NNTp was 6.0 (5.0 to 8.7), which was not significantly different.

Relief of headache-associated symptoms

Naproxen versus placebo

Three studies provided data on relief of nausea, photophobia, and phonophobia in comparison with placebo (Brandes 2007 Study 1; Brandes 2007 Study 2; Wentz 2008; Analysis 1.7). Too few participants experienced vomiting to allow any analysis of this symptom.

For all symptoms, naproxen was better than placebo; lower (better) NNTs were obtained for all three symptoms in comparisons with placebo. The higher dose of naproxen did not significantly affect the result.

Summary of results: relief of headache-associated symptoms at two hours

(Continued)

Intervention	Studies	Attacks with symptom present	Treatment (%)	Placebo (%)	Relative benefit (95% CI)	NNT (95% CI)
Nausea						
Naproxen 500/825 mg vs placebo	3	782	39	23	1.7 (1.4 to 2.1)	6.1 (4.4 to 11)
Naproxen 500 mg vs placebo	2	686	36	21	1.7 (1.3 to 2.2)	6.8 (4.7 to 12)
Photophobia						
Naproxen 500/825 mg vs placebo	3	1342	32	19	1.7 (1.4 to 2.1)	7.3 (5.5 to 11)
Naproxen 500 mg vs placebo	2	1185	31	18	1.7 (1.4 to 2.1)	7.7 (5.6 to 12)
Phonophobia						
Naproxen 500/825 mg vs placebo	3	1303	35	23	1.7 (1.4 to 2.0)	7.2 (5.3 to 11)
Naproxen 500 mg vs placebo	2	1146	32	20	1.6 (1.3 to 2.0)	8.1 (5.7 to 14)
CI: confidence interval; NNT: number needed to treat.						

Relief of functional disability

Two studies treating when pain was at least moderate (1348 participants, Brandes 2007 Study 1 and Brandes 2007 Study 2, reported in Landy 2007) reported on participants with functional disability at baseline and at two hours; 20% experienced complete relief of disability with naproxen 500 mg, and 9% with placebo. The relative benefit was 2.1 (1.6 to 2.8) (Analysis 1.8) and the NNT was 9.5 (7.0 to 15). There were no useful data on the higher naproxen dose.

Treating headaches with naproxen was significantly better than placebo for relief of functional disability.

Appendix 8. MT100 (naproxen sodium 500 mg + metoclopramide 16 mg) versus placebo

Outcome	Baseline pain	Studies	Attacks treated	Treatment (%)	Placebo or comparator (%)	Relative benefit (95% CI)	NNT (95% CI)
Headache relief at 2 h	≥ mod	4	1622	46	31	1.5 (1.3 to 1.7)	6.8 (5.1 to 9.9)
Sustained headache relief during the 24 h post dose	≥ mod	4	1622	33	20	1.6 (1.4 to 2.0)	7.5 (5.7 to 11)

CI: confidence interval; mod: moderate; NNT: number needed to treat.

Cochrane Database of Systematic Reviews

Data from Pozen 2005a; Pozen 2005b

WHAT'S NEW

Date	Event	Description
8 July 2020	Review declared as stable	See Published notes.

HISTORY

Protocol first published: Issue 11, 2011
Review first published: Issue 10, 2013

Date	Event	Description
29 May 2019	Amended	Contact details updated.
20 May 2015	Review declared as stable	This review will be re-assessed for updating in 2020. See Published notes.
20 December 2013	Amended	Minor changes made to definitions of 24-hour outcomes and Use of rescue medication in Appendix 1, and 95% confidence intervals added to NNTs in Abstract

CONTRIBUTIONS OF AUTHORS

SD and RAM wrote the protocol.

For the full review, SD and SL searched for studies, identified those for inclusion, and carried out data extraction. RAM checked data extraction. SL entered data into RevMan, and SD checked it. All authors were involved in analysis and writing the final review.

DECLARATIONS OF INTEREST

SOURCES OF SUPPORT

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

After discussion with headache specialists and editorial staff, and in line with Cochrane recommendations, we decided to limit our outcomes for acute migraine headache reviews in order to focus attention on the most important outcomes and to make them more readable for both clinicians and patients. For the majority of interventions we will now include two-hour pain-free and headache relief as primary outcomes, and 24-hour sustained pain-free, sustained headache relief, and adverse events as secondary outcomes. Pain-free headache relief outcomes at earlier time points will be included in special circumstances, if reported and relevant (eg if a 'fast acting' formulation is investigated). We have moved results for use of rescue medication and relief of headache-associated symptoms and functional disability to Appendix 7.

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

NOTES

Assessed for updating in 2015

In April 2015, we did not identify any potentially relevant new studies after a restricted search (electronic search strategy run in selected databases). The conclusions of this Cochrane Review, which last had a full search in May 2013, are therefore still considered up-to-date. The review will be assessed for further updating in 2020.

Assessed for updating in 2020

At July 2020 we are not aware of any potentially relevant studies likely to change the conclusions. This is not an active area of research and so this review has now been stabilised following discussion with the authors and editors. If appropriate we will update the review if new evidence likely to change the conclusions is published, or if standards change substantially which necessitates major revisions.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Inflammatory Agents, Non-Steroidal [*administration & dosage] [adverse effects]; Antiemetics [*administration & dosage]; Drug Therapy, Combination [methods]; Migraine Disorders [complications] [*drug therapy]; Naproxen [*administration & dosage] [adverse effects]; Nausea [complications] [*drug therapy]; Piperidines [administration & dosage]; Randomized Controlled Trials as Topic; Sumatriptan [administration & dosage]; Tryptamines [administration & dosage]; Vomiting [complications] [*drug therapy]

MeSH check words

Adult; Humans