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Sumatriptan plus naproxen for the treatment of acute migraine attacks in adults (Review)

Law S, Derry S, Moore RA

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[Intervention Review]

Sumatriptan plus naproxen for the treatment of acute migraine attacks in adults

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ABSTRACT

Background

This is an updated version of the original Cochrane review published in October 2013 on 'Sumatriptan plus naproxen for acute migraine attacks in adults'.

Migraine is a common disabling condition and a burden for the individual, health services, and society. It affects two to three times more women than men, and is most common in the age range 30 to 50 years. Effective abortive treatments include the triptan and non-steroidal anti-inflammatory classes of drugs. These drugs have different mechanisms of action and combining them may provide better relief. Sumatriptan plus naproxen is now available in combination form for the acute treatment of migraine.

Objectives

To determine the efficacy and tolerability of sumatriptan plus naproxen, administered together as separate tablets or taken as a fixed-dose combination tablet, compared with placebo and other active interventions in the treatment of acute migraine attacks in adults.

Search methods

For this update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) via *The Cochrane Register of Studies Online* (CRSO) to 28 October 2015, MEDLINE (via Ovid) from 1946 to 28 October 2015, and EMBASE (via Ovid) from 1974 to 28 October 2015, and two online databases (www.gsk-clinicalstudyregister.com and www.clinicaltrials.gov). We also searched the reference lists of included studies and relevant reviews.

Selection criteria

We included randomised, double-blind, placebo- or active-controlled studies, with at least 10 participants per treatment arm, using sumatriptan plus naproxen 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 ratio and numbers needed to treat for an additional beneficial outcome (NNT) or for an additional harmful outcome (NNH) compared with placebo or a different active treatment.

Main results

For this update we identified one new study (43 participants), but it did not contribute any data for analysis. The review included 13 studies using sumatriptan 85 mg or 50 mg plus naproxen 500 mg to treat attacks of mild, moderate, or severe pain intensity. Twelve studies

contributed data for analyses: 3663 participants received combination treatment, 3682 placebo, 964 sumatriptan, and 982 naproxen. We judged only one small study to be at high risk of bias for any of the criteria evaluated; it did not contribute to any analyses.

Overall, the combination was better than placebo for the primary outcomes of pain-free and headache relief at two hours. The NNT for pain-free at two hours was 3.1 (95% confidence interval 2.9 to 3.5) when the baseline pain was mild (50% response with sumatriptan plus naproxen compared with 18% with placebo), and 4.9 (4.3 to 5.7) when baseline pain was moderate or severe (28% with sumatriptan plus naproxen compared with 8% with placebo) (high quality evidence). Using 50 mg of sumatriptan, rather than 85 mg, in the combination did not significantly change the result. Treating early, when pain was still mild, was significantly better than treating once pain was moderate or severe for pain-free responses at two hours and during the 24 hours post dose. Adverse events were mostly mild or moderate in severity and rarely led to withdrawal; they were more common with the combination than with placebo (moderate quality evidence).

Where the data allowed direct comparison, combination treatment was superior to either monotherapy, but adverse events were less frequent with naproxen than with sumatriptan (moderate quality evidence).

Authors' conclusions

The conclusions of this review were not changed. Combination treatment was effective in the acute treatment of migraine headaches. The effect was greater than for the same dose of either sumatriptan or naproxen alone, but additional benefits over sumatriptan alone were not large. More participants achieved good relief when medication was taken early in the attack, when pain was still mild. Adverse events were more common with the combination and sumatriptan alone than with placebo or naproxen alone.

PLAIN LANGUAGE SUMMARY

Sumatriptan plus naproxen for acute migraine attacks in adults

Bottom line

The combination of sumatriptan plus naproxen was useful for treating migraine attacks in the studies we found. It was not a lot better than using sumatriptan alone, but it was much better than using naproxen alone. Attacks were more successfully treated when medication was taken early, when pain was mild.

Background

Migraine is a complex condition with a wide variety of symptoms. It affects two to three times more women than men, and is most common in the age range 30 to 50 years. For many people, the main feature is a painful headache. Other symptoms include disturbed vision; sensitivity to light, sound, and smells; feeling sick; and vomiting.

Both nonsteroidal anti-inflammatory drugs (NSAIDs) and the triptan class of drugs are used to treat migraine headaches. This review examined how well naproxen (an NSAID) and sumatriptan (a triptan) work when combined. The combination tablet is not available in most countries, but separate tablets are widely available and can be taken together.

Study characteristics

On 28 October 2015, we looked for clinical trials using sumatriptan plus naproxen to treat migraine headache in adults. People were given either a combination of sumatriptan and naproxen, sumatriptan only, naproxen only, or a placebo (dummy) treatment. They did not know which treatment they were taking, and nor did the health professionals looking after them.

Key results

We found 13 studies, of which 12 (with about 9300 people) provided information on how well the combination treatment worked.

The combination of sumatriptan plus naproxen was better than placebo for relieving acute migraine attacks in adults. When the starting headache intensity was mild, 5 in 10 (50%) of people treated with the combination were pain-free at two hours compared with about 2 in 10 (18%) with placebo. Almost 6 in 10 (58%) people with moderate or severe pain who were treated with the combination had pain reduced to mild or none at two hours, compared with 3 in 10 (27%) with placebo. The combination was also better than the same dose of either drug given alone in these people. Results were 5 in 10 (52%) people with sumatriptan alone or about 4 in 10 (44%) with naproxen alone.

The combination was better than placebo or either drug alone for relief of other migraine symptoms (nausea, sensitivity to light or sound) and loss of ability to function normally. Adverse events of dizziness, tingling or burning of the skin, sleepiness (somnolence), nausea, indigestion (dyspepsia), dry mouth, and chest discomfort were more common with sumatriptan (alone or in combination) than with placebo or naproxen. They were generally of mild to moderate severity and rarely led to withdrawal from the studies.

Quality of the evidence

The studies were carried out to high standards and were generally large enough to give reliable results, so that most of the results for efficacy were of high quality. Results for adverse events were downgraded to moderate quality because there were fewer events.

Summary of findings 1. Sumatriptan 50 mg or 85 mg plus naproxen 500 mg compared with placebo for migraine headache

Sumatriptan 50 mg or 85 mg plus naproxen 500 mg compared with placebo for migraine headache

Patient or population: adults with migraine headache - moderate or severe and mild baseline pain

Settings: community

Intervention: sumatriptan 50 mg or 85 mg plus naproxen 500 mg

Comparison: placebo

Outcomes	Probable outcome with comparator	Probable outcome with intervention	NNT or NNH (95% CI)	No. of studies, attacks, events	Quality of the evidence (GRADE)	Comments
Pain-free response at 2 h for moderate to severe baseline pain	77 in 1000	280 in 1000	RR 3.7 (2.8 to 4.5) NNT 4.9 (4.3 to 5.7)	4 studies, 2596 attacks, 462 events	High	Adequate numbers of studies and attacks, study quality good, consistency of response
Pain-free response at 2 h for mild baseline pain	180 in 1000	500 in 1000	RR 2.8 (2.4 to 3.1) NNT 3.1 (2.9 to 3.5)	8 studies, 3395 attacks, 1252 events	High	Adequate numbers of studies and attacks, study quality good, consistency of response
Headache relief at 2 h for moderate to severe baseline pain	270 in 1000	580 in 1000	RR 2.2 (2.0 to 2.4) NNT 3.2 (2.9 to 3.6)	4 studies, 2596 attacks, 1107 events	High	Adequate numbers of studies and attacks, study quality good, consistency of response
Sustained pain-free during the 24 h post dose for moderate to severe baseline pain	60 in 1000	200 in 1000	RR 3.4 (2.7 to 4.4) NNT 7.9 (5.9 to 8.5)	4 studies, 2596 attacks, 339 events	Moderate	Adequate numbers of studies and attacks, study quality good, consistency of response. Downgraded because of threat from potential publication bias with modest effect size and modest number of events
Sustained pain-free during the 24 h post dose for mild baseline pain	120 in 1000	370 in 1000	RR 3.0 (2.6 to 3.6) NNT 4.1 (3.7 to 4.6)	8 studies, 3396 attacks, 907 events	High	Adequate numbers of studies and attacks, study quality good, consistency of response

Sustained headache relief during the 24 h post dose for moderate or severe baseline pain	160 in 1000	430 in 1000	RR 2.6 (2.3 to 3.0) (NNT 3.8 (3.4 to 4.3)	4 studies, 2596 attacks, 768 events	High	Adequate numbers of studies and attacks, study quality good, consistency of response
At least 1 AE during treatment for moderate to severe baseline pain	120 in 1000	210 in 1000	RR 2.0 (1.6 to 2.4) NNH 11 (8.3 to 15)	4 studies, 2793 attacks, 465 events	Moderate	Adequate numbers of studies and attacks, study quality good, consistency of response. Downgraded because of threat from potential publication bias with modest effect size
At least 1 AE during treatment for mild baseline pain	82 in 1000	140 in 1000	RR 1.5 (1.2 to 1.9) NNH 18 (13 to 30)	6 studies, 2823 attacks, 329 events	Moderate	Adequate numbers of studies and attacks, study quality good, consistency of response. Downgraded because of threat from potential publication bias with modest effect size and modest number of events
Serious AE (all levels of baseline pain)	No events	1 event possibly related to intervention	-	-	-	-

AE: adverse event; **CI:** confidence interval; **NNT:** number needed to treat for an additional beneficial outcome; **NNH:** number needed to treat for an additional harmful outcome; **RR:** risk ratio.

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.

BACKGROUND

This is an update of a review first published in October 2013 (Law 2013a).

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). Recent 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 (98%) migraineurs used acute treatments for attacks, with 49% using over-the-counter (OTC) medication only, 20% using prescription medication, and 29% using both. OTC medications included aspirin, other non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol (acetaminophen), and paracetamol plus 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

The symptomatic treatment of migraine advanced significantly with the development of the triptan class of drugs, of which sumatriptan was the first. Sumatriptan is available as 50 mg and 100 mg oral tablets (maximum dose 300 mg in 24 hours) and also as a subcutaneous injection (6 mg dose, maximum 12 mg in 24 hours), intranasal spray (20 mg, maximum 40 mg in 24 hours), and rectal suppositories (12.5 mg and 25 mg). In most parts of the world it is available only by prescription, but in some countries it is available to the public without prescription. Naproxen is an NSAID first marketed in the mid-1970s, with confirmed efficacy in acute (Derry 2009) and chronic (Moore 2010a; Moore 2010b) pain, and limited efficacy in migraine (Law 2013b). 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. Both sumatriptan and naproxen are widely available generically and are marketed by a very large number of companies worldwide (http://www.drugs.com/international/sumatriptan.html and www.drugs.com/international/naproxen.html (accessed 31 March 2016)).

A fixed-dose combination tablet (trade name Trexima or Treximet; GlaxoSmithKline) containing sumatriptan 85 mg plus naproxen 500 mg is now available by prescription in the USA. It appears not to be available in Europe as of October 2015; we were unable to establish availability and licensing in other parts of the world. Compared with the individual components, the combination is expensive, and there was a very large increase in price in October 2014, to over USD 70 per tablet (GoodRx 2015; Wikipedia 2015).

In order to establish whether sumatriptan plus naproxen is an effective analgesic combination 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 attack early while pain is mild, and using a low dose initially, with a second dose if response is inadequate.

How the intervention might work

The challenge in optimising therapy for acute migraine headaches is in providing broad coverage of the multiple pathogenic processes

involved, which are thought to include several neural pathways becoming sequentially activated and sensitised as an attack develops (Goadsby 2002).

Early in an attack, trigeminal nerve endings release vasoactive and inflammatory substances such as calcitonin gene-related peptide and kinins. Calcitonin gene-related peptide causes meningeal vasodilation, and kinins induce release of inflammatory prostaglandins. The resulting vascular and meningeal inflammation stimulates trigeminal nociceptors and activates central pathways via ascending pain pathways. Prolonged nociceptive input causes central foci to fire in a sustained continuous manner causing a symptomatic migraine attack. This is characteristic of the central sensitisation hypothesis (Burstein 2001).

Sumatriptan is a 5-HT_1 agonist, selectively targeting the 5-HT (serotonin) 1B and 1D receptors. It is suggested that it inhibits synaptic transmission from the periphery before central sensitisation occurs. Three putative mechanisms of therapeutic action are involved (Ferrari 2002):

- vasoconstriction of dilated meningeal blood vessels;
- inhibition of the release of vasoactive neuropeptides from perivascular trigeminal sensory neurons;
- reduction of pain signal transmission in the trigeminal dorsal horn.

Non-steroidal anti-inflammatory drugs (NSAIDs) block the effect of cyclo-oxygenase on arachidonic acid, which is responsible for the synthesis of prostaglandins. 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 a reversible inhibitor of cyclo-oxygenase. Unlike the triptans, which exert their effect peripherally, 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). Because multiple mechanisms are involved in migraine, multi-mechanism targeted therapy with sumatriptan plus naproxen may confer advantages over conventional monotherapy.

Why it is important to do this review

Other Cochrane reviews of treatments for acute migraine in adults have shown that oral sumatriptan had good efficacy (Derry 2012), and naproxen alone had limited efficacy (Law 2013b). It is important to assess and analyse the data now available for combination therapy involving these two agents, particularly in the light of recent research showing that fixed-dose combinations of analgesics generally provide enhanced analgesic efficacy in acute pain and migraine when compared with any single drug in the combination (Moore 2012).

OBJECTIVES

To determine the efficacy and tolerability of sumatriptan plus naproxen, administered together as separate tablets or taken as a fixed-dose combination tablet, compared with placebo and other active interventions in the treatment of acute migraine attacks in adults.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised, double-blind, placebo- or active-controlled studies using sumatriptan plus 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 (≥ 48 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), and excluded trials evaluating treatments for chronic migraine. We applied 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. We provided details on any prophylactic therapy prescribed or allowed in the Characteristics of included studies table.

Types of interventions

We included studies in which self administered sumatriptan plus naproxen (as separate tablets administered together, or as a fixed-dose combination tablet) was used to treat a migraine headache episode. We applied no restrictions on dose, dosing regimen (eg single dose versus optional second dose), or timing of the first dose in relation to headache intensity (eg taking the first dose when pain was of moderate to severe intensity versus when the pain was mild).

A placebo comparator is essential to demonstrate that sumatriptan plus 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

Primary outcomes

In selecting the main outcome measures for this review, we considered scientific rigour, availability of data, and patient preferences (Lipton 1999). Patients with acute migraine headaches have rated complete 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), the main outcomes that we considered were:

- 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 also collected data for pain-free and headache relief outcomes at one hour if reported.

Secondary outcomes

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

Other outcomes

We also collected data for other outcomes, where reported, 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 provider). We accepted the following pain measures for the main efficacy outcomes:

- 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, and 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 databases.

- the Cochrane Central Register of Controlled Trials (CENTRAL), *The Cochrane Library,* (Issue 6 of 12, 2013 for the original review, and on 28 October 2015 via CRSO for this update).
- MEDLINE (via Ovid) (1946 to 28 October 2015).
- EMBASE (via Ovid) (1974 to 28 October 2015).

See Appendix 2, Appendix 3, and Appendix 4 for the search strategies used for this update for CENTRAL (via CRSO), 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). For the original review we contacted the manufacturer of the fixed-dose combination agent (GlaxoSmithKline) for information about both published and unpublished data, but no additional studies were identified in their response. We did not search grey literature and 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. Disagreements were settled by discussion with a third review author.

Data extraction and management

Two review authors independently extracted data from included studies using a standard data extraction form. We settled disagreements by discussion with a third review author. One review author entered data into Review Manager 5 (RevMan 2014).

Assessment of risk of bias in included studies

We used the Oxford Quality Score as the basis for inclusion (Jadad 1996), 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* (Chapter 8.5, 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: 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 (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 (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 (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: 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 - 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 ratios (RR) to establish statistical difference. Numbers needed to treat for an additional beneficial outcome (NNT) and pooled percentages were used 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 sumatriptan plus 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 occur with sumatriptan plus 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 planned to analyse data using the individual participant as the unit of analysis. In cross-over studies we planned to use only first-period data where possible, but where that was not provided, we used headache episode as the unit of analysis and treated the results as if they were parallel group results. We have commented on this.

Dealing with missing data

The most likely source of missing data was in cross-over studies. If there had been substantial missing data in any study, we planned sensitivity analyses to investigate their effects, but this was not an issue.

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.

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 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 of 6 or greater for headache relief at two hours.

Data synthesis

We analysed studies using a single dose of sumatriptan plus naproxen in established pain of at least moderate intensity separately from studies in which medication was taken before pain became 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). Risk ratio (relative benefit or harm) 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 to determine significant differences between NNT, NNTp, and NNH for different groups in subgroup and sensitivity analyses (Tramèr 1997).

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

We have included a 'Summary of findings' table as set out in the PaPaS author guide (PaPaS 2012), and recommended in the Cochrane Handbook (Chapter 4.6.6, Higgins 2011; Summary of findings 1). The table includes outcomes of pain-free at two hours, sustained pain-free at 24 hours, and at least one adverse event for participants treating mild pain, and pain-free or mild pain at 2 hours, sustained pain-free at 24 hours, sustained headache relief at 24 hours, and at least one adverse event for participants treating moderate or severe pain. We combined results for all levels of baseline pain for participants with serious adverse events due to the small amount of data. We used the GRADE approach to assess the quality of evidence related to each of the key outcomes, and report our judgement on the quality of the evidence in the Summary of findings tables (chapter 12.2, Higgins 2011; Appendix 5).

Subgroup analysis and investigation of heterogeneity

Issues for potential subgroup analysis were dose, timing of doses, route of administration, and multiple dosing strategies. A minimum of two studies and 200 participants had to be available for any subgroup analysis.

Sensitivity analysis

We planned a sensitivity analysis for menstrual migraine versus non-menstrual migraine. A minimum of two studies and 200 participants had to be available for any sensitivity analysis.

RESULTS

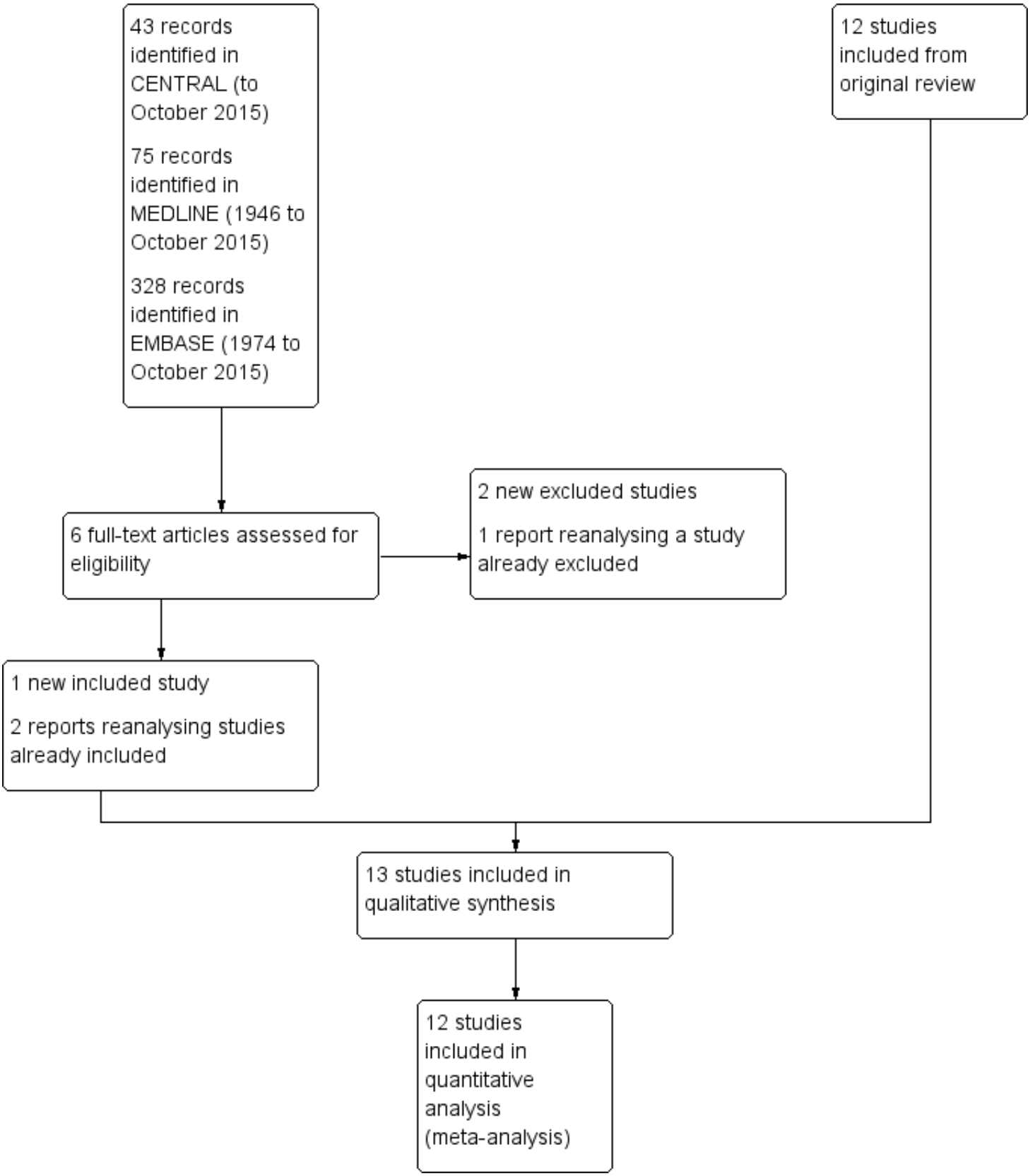
Description of studies

Results of the search

For the earlier review we identified 18 potentially relevant studies, of which we included 12 and excluded six. For this update we identified a further six potentially relevant studies. One of these studies satisfied our inclusion criteria (Calhoun 2014), two were secondary analyses of studies that were already included (Landy 2014 from Lipton 2009 Study 1 and Lipton 2009 Study 2, Martin 2014 from Mannix 2009 Study 1 and Mannix 2009 Study 2), one was a full publication of an already excluded study previously identified in a clinical trial registry (Silberstien 2014 from TRX107563), and we excluded two studies (Cady 2014; Edwards 2013).

Figure 1 shows the results of the updated searches.

Figure 1. Study flow diagram.



Included studies

Thirteen studies (with data reported in eight primary publications) satisfied all inclusion criteria and are included in this review. Seven studies used a parallel group design (Brandes 2007 Study 1; Brandes 2007 Study 2; Mannix 2009 Study 1; Mannix 2009 Study 2; Silberstein 2008 Study 1; Silberstein 2008 Study 2; Smith 2005), and six studies were cross-over in design (Calhoun 2014; Lipton 2009 Study 1; Lipton 2009 Study 2; Mathew 2009 Study 1; Mathew 2009 Study 2; TRX109011/13). TRX109011/13 was available only as a clinical trial summary with results at the time that initial data extraction was carried out, but has subsequently been published in a peer-reviewed journal (Derosier 2012). For two of the cross-over studies treating more than one episode with the same medication, we used data from the first period (Lipton 2009 Study 1; Lipton 2009 Study 2). The third cross-over study treating more than one episode with the same medication reported only a percentage response for active and placebo treatments, and it was not clear what denominator had been used, so we were unable to use these data in the analysis (Calhoun 2014). First period only data were not reported for the other three cross-over studies (Mathew 2009 Study 1; Mathew 2009 Study 2; TRX109011/13), so we used combined data for analyses, with a post-hoc sensitivity analysis in addition to those sensitivity analyses outlined in the protocol. In nine studies, medication was to be taken early in the attack, while PI was still mild (Calhoun 2014; Lipton 2009 Study 1; Lipton 2009 Study 2; Mannix 2009 Study 1; Mannix 2009 Study 2; Mathew 2009 Study 1; Mathew 2009 Study 2; Silberstein 2008 Study 1; Silberstein 2008 Study 2), and in the remaining four studies when it was moderate or severe (Brandes 2007 Study 1; Brandes 2007 Study 2; Smith 2005; TRX109011/13). No studies employed multiple dosing strategies for a single attack.

Two further publications reported data on functional disability that were not reported in the primary publications; Landy 2007 for Brandes 2007 Study 1 and Brandes 2007 Study 2 and Taylor 2007 for Silberstein 2008 Study 1 and Silberstein 2008 Study 2. Other publications reported satisfaction, productivity, and functional disability outcomes for participants in Mannix 2009 Study 1 and Mannix 2009 Study 2 (Cady 2011), and in Lipton 2009 Study 1 and Lipton 2009 Study 2 (Landy 2014). Martin 2014 reported a pooled analysis of relief of menstrual symptoms in Mannix 2009 Study 1 and Mannix 2009 Study 2, but this was not of relevance to this review.

All studies were multicentre except Calhoun 2014, and all diagnosed migraine (with or without aura) according to IHS criteria. People with frequent migraine headaches (more than six or eight attacks per month) were excluded. In Calhoun 2014, people with more than eight attacks per month or more than 15 days per month with either headache or neck pain were excluded. Most studies required that participants had previously tolerated treatment with a triptan or had no contraindications, or both, but Mathew 2009 Study 1 and Mathew 2009 Study 2 included participants who had specifically been previous poor responders to triptans with a short half-life, including sumatriptan, and TRX109011/13 required that participants had previous experience using barbiturate-containing medicines. In all studies, participants self treated their headaches at home. Two studies included only participants with menstrual migraine (Mannix 2009 Study 1; Mannix 2009 Study 2). Overall, the mean age of participants ranged from 36 to 43 years, and between 85% and 100% were female. Generally, participants were eligible for inclusion if they were using stable prophylactic medication provided it was not a triptan, methysergide, or ergot derivative. Cross-over studies where we used combined data across treatment periods (Mathew 2009 Study 1; Mathew 2009 Study 2; TRX109011/13) had adequate washout periods between treatments of at least one week. The washout period was not specified in two other cross-over studies (Lipton 2009 Study 1; Lipton 2009 Study 2); for these, first period only data were available and were used for analyses. Calhoun 2014 specified only that the preceding day was completely free of both headache and neck pain.

Twelve studies gave sumatriptan 85 mg plus naproxen 500 mg formulated as a combination tablet, while Smith 2005 gave sumatriptan 50 mg plus naproxen 500 mg as separate tablets taken together. All studies compared sumatriptan plus naproxen versus placebo, and three studies included treatment arms using sumatriptan 85 mg (Brandes 2007 Study 1; Brandes 2007 Study 2) or 50 mg (Smith 2005) and naproxen 500 mg alone. One study compared the combination with placebo and a butalbital-containing active comparator (TRX109011/13); there were insufficient data for a head-to-head analysis of the active comparator from this single trial. There were no other active comparators. In total, 3663 participants who took sumatriptan plus naproxen were included in safety analyses for adverse events; 3682 took placebo, 964 took sumatriptan alone, 982 took naproxen alone, and 304 took a combination medication containing butalbital 50 mg, paracetamol (acetaminophen) 325 mg, and caffeine 40 mg. The number included in efficacy analyses was slightly lower because some participants were excluded from these analyses due to protocol violations, and Calhoun 2014 did not provide data for pooled analyses.

The outcomes reported by individual studies are listed in the Characteristics of included studies table. All studies included in the pooled analyses measured headache PI using a standard 4-point scale, and evaluated pain-free response at two hours and sustained pain-free during the 24 hours post dose as the primary outcome measures. Of the four studies treating headache of moderate or severe intensity, all measured headache relief at two hours and sustained headache relief during the 24 hours post dose (Brandes 2007 Study 1; Brandes 2007 Study 2; Smith 2005; TRX109011/13), with Smith 2005 also reporting headache relief at the earlier time of one hour. All studies reported on adverse events. Calhoun 2014 reported the outcome 'pain relief' as being a 2-point decrease in pain intensity, but did not specify the tool used to measure pain intensity.

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

Excluded studies

We excluded eight studies (nine publications) (Cady 2014; Edwards 2013; Krymchantowski 2000; Landy 2009; Smith 2007; TRX107563 (and Silberstein 2014); White 2011; Winner 2007). Details are in the Characteristics of excluded studies table.

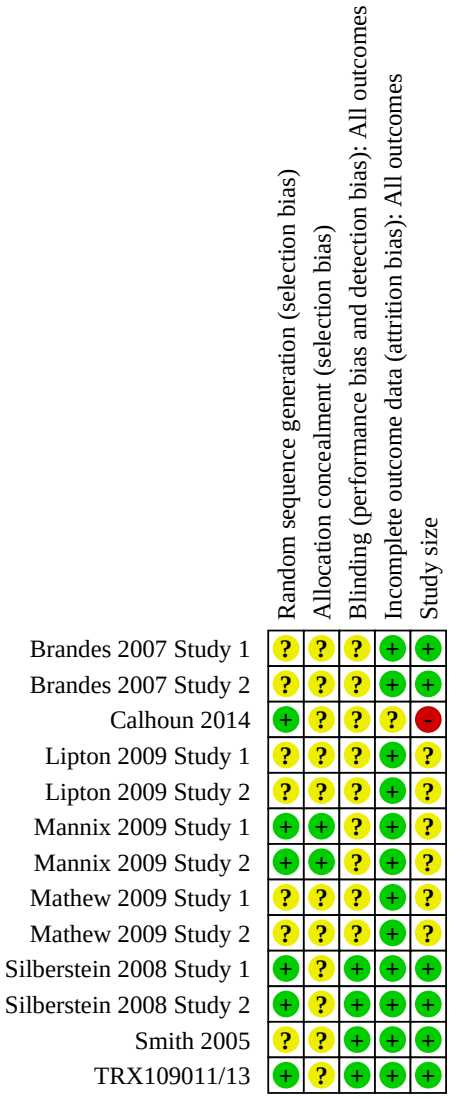
Risk of bias in included studies

Methodological quality, assessed using the Oxford Quality Scale, was good in all studies. Three studies scored 5/5 (Silberstein 2008 Study 1; Silberstein 2008 Study 2; TRX109011/13), three scored 4/5 (Mannix 2009 Study 1; Mannix 2009 Study 2; Smith 2007), and seven scored 3/5 (Brandes 2007 Study 1; Brandes 2007 Study 2; Calhoun 2014; Lipton 2009 Study 1; Lipton 2009 Study 2; Mathew 2009 Study 1; Mathew 2009 Study 2). Points were lost mainly due to failure to

report the method of randomisation or blinding adequately. Full details are in the Characteristics of included studies table.

We also completed a 'Risk of bias' assessment. Studies were generally of a very high standard, but frequently failed to report details of the methods used to reduce bias (randomisation, allocation concealment, blinding). It is likely that this is an omission in reporting rather than a deficiency in methods (Figure 2).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

All studies stated that they were randomised but only six adequately described the methods used to generate the random sequence (Calhoun 2014; Mannix 2009 Study 1; Mannix 2009 Study 2; Silberstein 2008 Study 1; Silberstein 2008 Study 2; TRX109011/13) and only two described the method used to conceal allocation (Mannix 2009 Study 1; Mannix 2009 Study 2).

Blinding

All studies reported that they were double-blind, but only four adequately described the methods used to maintain blinding (Silberstein 2008 Study 1; Silberstein 2008 Study 2; Smith 2005; TRX109011/13).

Incomplete outcome data

All studies accounted for all participants except Calhoun 2014, in which the denominator used for calculating per cent response was

unclear. This study did not contribute to any analyses. Other studies did not have substantial amounts of missing data.

Other potential sources of bias

We judged Calhoun 2014 to be at high risk of bias due to its small size (fewer than 50 participants per treatment arm), but this study did not contribute to any analyses. We judged the remaining studies to be at unknown or low risk of bias due to their size.

Effects of interventions

See: **Summary of findings 1** Sumatriptan 50 mg or 85 mg plus naproxen 500 mg compared with placebo for migraine headache

Studies treating headache early, when pain was still mild, were analysed separately from those treating only once pain was of moderate or severe intensity. For analysis, we chose to combine results from the study using sumatriptan 50 mg plus naproxen 500 mg, given as separate tablets, with studies that used sumatriptan 85 mg plus naproxen 500 mg, given as a combined formulation. We carried out sensitivity analyses to determine the effect of the combined formulation alone.

Details of the main efficacy outcomes in individual studies are in Appendix 6, and of adverse events and withdrawals are in Appendix 7. Results for pain-free and headache relief outcomes are summarised in Summary of results: Pain-free and headache relief. A summary of the main results, together with a judgement on the quality of the evidence for each outcome, is presented in Summary of findings 1.

Pain-free at two hours

Sumatriptan plus naproxen versus placebo

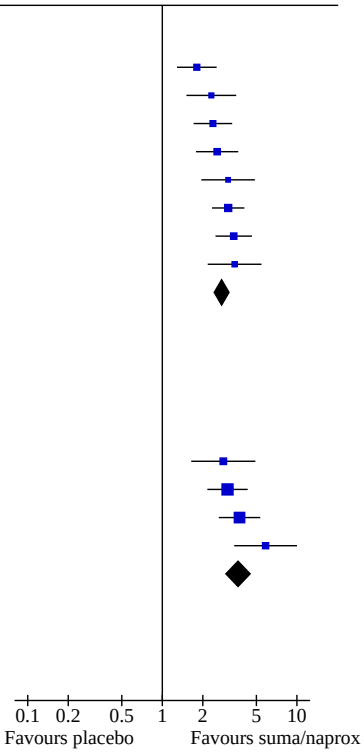
Mild baseline pain

Eight studies (3395 attacks) provided data for early use of the combined formulation, compared with placebo, when pain was still mild (Lipton 2009 Study 1; Lipton 2009 Study 2; Mannix 2009 Study 1; Mannix 2009 Study 2; Mathew 2009 Study 1; Mathew 2009 Study 2; Silberstein 2008 Study 1; Silberstein 2008 Study 2).

- The proportion of attacks pain-free at two hours with sumatriptan plus naproxen 85/500 mg was 50% (1008/2025; range 40% to 52%).
- The proportion of attacks pain-free at two hours with placebo was 18% (244/1370; range 14% to 23%).
- The relative benefit of treatment compared with placebo was 2.8 (95% CI 2.4 to 3.1) (Figure 3); the NNT was 3.1 (95% CI 2.9 to 3.5).

Figure 3. Forest plot of comparison: 1 Sumatriptan plus naproxen versus placebo, outcome: 1.1 Pain-free at two hours.

Study or Subgroup	Suma/naprox Events	Suma/naprox Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Mild baseline pain						
Mannix 2009 Study 1	63	151	37	160	13.5%	1.80 [1.28 , 2.53]
Mathew 2009 Study 1	54	136	23	134	8.7%	2.31 [1.51 , 3.54]
Mannix 2009 Study 2	79	151	35	159	12.8%	2.38 [1.71 , 3.31]
Lipton 2009 Study 1	230	443	25	123	14.7%	2.55 [1.78 , 3.67]
Mathew 2009 Study 2	59	134	19	133	7.2%	3.08 [1.95 , 4.87]
Silberstein 2008 Study 1	146	280	50	296	18.3%	3.09 [2.34 , 4.07]
Silberstein 2008 Study 2	141	276	39	259	15.1%	3.39 [2.48 , 4.63]
Lipton 2009 Study 2	236	454	16	106	9.7%	3.44 [2.17 , 5.46]
Subtotal (95% CI)		**2025**		**1370**	**100.0%**	**2.76 [2.43 , 3.13]**
Total events:	1008		244			
Heterogeneity: Chi² = 11.07, df = 7 (P = 0.14); I² = 37%						
Test for overall effect: Z = 15.73 (P < 0.00001)						
1.1.2 Moderate/severe baseline pain						
TRX109011/13	45	317	16	320	16.0%	2.84 [1.64 , 4.92]
Brandes 2007 Study 2	107	362	37	382	36.2%	3.05 [2.16 , 4.31]
Brandes 2007 Study 1	125	364	33	360	33.4%	3.75 [2.63 , 5.34]
Smith 2005	85	250	14	241	14.3%	5.85 [3.42 , 10.01]
Subtotal (95% CI)		**1293**		**1303**	**100.0%**	**3.65 [2.97 , 4.49]**
Total events:	362		100			
Heterogeneity: Chi² = 4.83, df = 3 (P = 0.18); I² = 38%						
Test for overall effect: Z = 12.24 (P < 0.00001)						
Test for subgroup differences: Chi² = 5.13, df = 1 (P = 0.02), I² = 80.5%						



Calhoun 2014 reported a response rate of 64% with sumatriptan plus naproxen and 33% with placebo for this outcome in participants who experienced fewer than eight days/month with migraine headache or 15 days/month with migraine headache **or** neck pain. Data from six attacks were missing due to the participant

being asleep at two hours; these attacks were not counted as 'pain-free at two hours' responses.

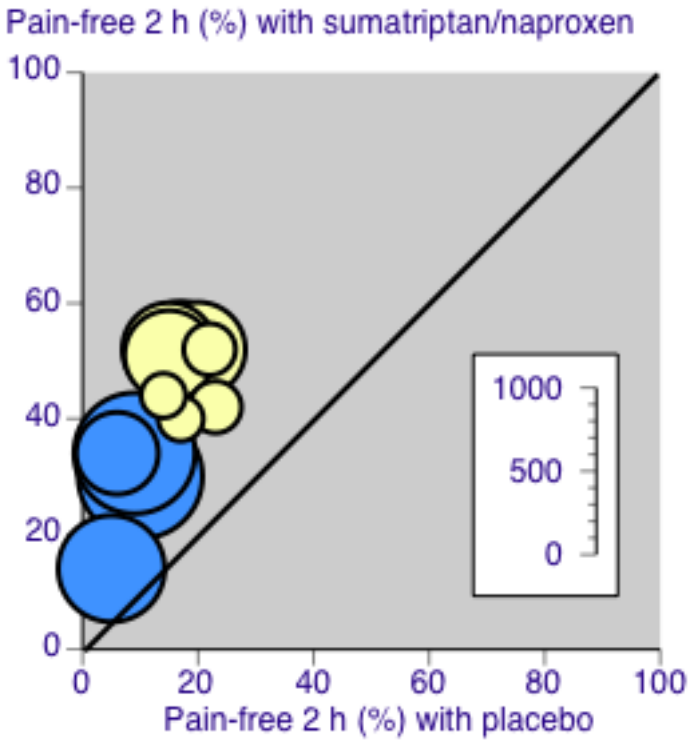
Moderate or severe baseline pain

Four studies (2596 attacks) provided data for use of either the combined formulation (Brandes 2007 Study 1; Brandes 2007 Study 2; TRX109011/13), or separate tablets (Smith 2005), compared with placebo, when pain was moderate or severe.

- The proportion of attacks pain-free at two hours with sumatriptan plus naproxen 50 to 85/500 mg was 28% (362/1293; range 14% to 34%).
- The proportion of attacks pain-free at two hours with placebo was 7.7% (100/1303; range 5% to 10%).
- The relative benefit of treatment compared with placebo was 3.7 (95% CI 3.0 to 4.5) (Figure 3); the NNT was 4.9 (95% CI 4.3 to 5.7).
- For sumatriptan plus naproxen 85/500 mg only (excluding the 50/500 mg dose), the NNT was 5.4 (95% CI 4.6 to 6.5), which was not significantly different from the NNT for the combined analysis.

Treating headache early, when pain was still mild, was significantly better than treating once pain was of moderate or severe intensity (z = 5.548; P value < 0.00001). A L'Abbé plot shows no evidence of heterogeneity within each group (Figure 4).

Figure 4. L'Abbé plot showing results for sumatriptan plus naproxen versus placebo for pain-free at two hours. Each circle represents a different study; blue circles are studies with moderate or severe baseline pain and cream circles are mild baseline pain; size of circle is proportional to size of study; diagonal is line of equivalence.



Sumatriptan plus naproxen versus sumatriptan or naproxen alone

Three studies provided data for use of either the combined formulation (Brandes 2007 Study 1; Brandes 2007 Study 2) or separate tablets (Smith 2005), compared with sumatriptan alone (1925 participants) or naproxen alone (1944 participants), when pain was moderate or severe.

- The proportion of participants pain-free at two hours with sumatriptan plus naproxen 50 to 85/500 mg was 32% (317/976; range 30% to 34%).
- The proportion of participants pain-free at two hours with sumatriptan alone was 23% (217/949; range 20% to 25%).
- The proportion of participants pain-free at two hours with naproxen alone was 16% (155/968; range 15% to 18%).
- The relative benefit of the combination compared with sumatriptan alone was 1.4 (95% CI 1.2 to 1.7) (Analysis 2.1); the NNT was 10 (95% CI 7.4 to 18).
- The relative benefit of the combination compared with naproxen alone was 2.0 (95% CI 1.7 to 2.4) (Analysis 3.1); the NNT was 6.1 (95% CI 5.0 to 7.9).

The combination was significantly better than either sumatriptan or naproxen alone.

Headache relief at two hours

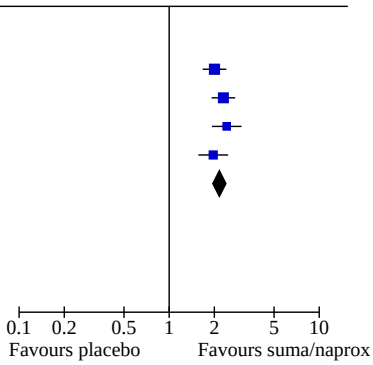
Sumatriptan plus naproxen versus placebo

Four studies (2596 attacks) provided data for use of either the combined formulation (Brandes 2007 Study 1; Brandes 2007 Study 2; TRX109011/13), or separate tablets (Smith 2005), compared with placebo, when pain was moderate or severe.

- The proportion of attacks with headache relief at two hours with sumatriptan plus naproxen 50 to 85/500 mg was 58% (755/1293; range 47% to 65%).
- The proportion of attacks with headache relief at two hours with placebo was 27% (352/1303; range 24% to 29%).
- The relative benefit of treatment compared with placebo was 2.2 (95% CI 2.0 to 2.4); the NNT was 3.2 (95% CI 2.9 to 3.6) (Figure 5).
- For sumatriptan plus naproxen 85/500 mg alone (excluding the 50/500 mg dose) the NNT was 3.4 (95% CI 3.0 to 3.9), which was not significantly different from the NNT for the combined analysis.

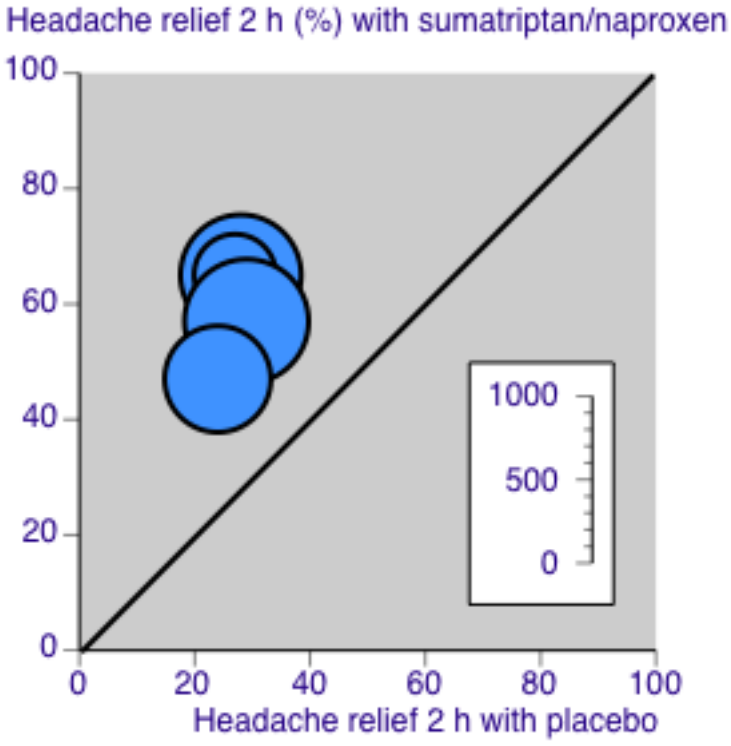
Figure 5. Forest plot of comparison: 1 Sumatriptan plus naproxen versus placebo, outcome: 1.2 Headache relief at two hours.

Study or Subgroup	Suma/naprox Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Moderate/severe baseline pain						
Brandes 2007 Study 1	207	362	109	382	30.3%	2.00 [1.67 , 2.40]
Brandes 2007 Study 2	237	364	102	360	29.3%	2.30 [1.92 , 2.75]
Smith 2005	163	250	65	241	18.9%	2.42 [1.93 , 3.03]
TRX109011/13	148	317	76	320	21.6%	1.97 [1.56 , 2.47]
Subtotal (95% CI)		**1293**		**1303**	**100.0%**	**2.16 [1.95 , 2.39]**
Total events:	755		352			
Heterogeneity: Chi² = 2.70, df = 3 (P = 0.44); I² = 0%						
Test for overall effect: Z = 15.05 (P < 0.00001)						
Test for subgroup differences: Not applicable						



A L'Abbé plot showed no evidence of heterogeneity between the studies (Figure 6).

Figure 6. L'Abbé plot showing results for sumatriptan plus naproxen versus placebo for headache relief at two hours in studies with moderate or severe baseline pain. Each circle represents a different study; size of circle is proportional to size of study; diagonal is line of equivalence.



Sumatriptan plus naproxen versus sumatriptan or naproxen alone

Three studies provided data for use of either the combined formulation (Brandes 2007 Study 1; Brandes 2007 Study 2), or separate tablets (Smith 2005), compared with sumatriptan alone (1925 participants) or naproxen alone (1944 participants), when pain was moderate or severe.

- The proportion of participants experiencing headache relief at two hours with sumatriptan plus naproxen 50 to 85/500 mg was 62% (607/976; range 57% to 65%).
- The proportion of participants experiencing headache relief at two hours with sumatriptan alone was 52% (493/949; range 49% to 55%).
- The proportion of participants experiencing headache relief at two hours with naproxen alone was 44% (426/968; range 43% to 45%).
- The relative benefit of the combination compared with sumatriptan alone was 1.2 (95% CI 1.1 to 1.3); the NNT was 9.8 (95% CI 6.8 to 17) (Analysis 2.2).
- The relative benefit of the combination compared with naproxen alone was 1.4 (95% CI 1.3 to 1.5); the NNT was 5.5 (95% CI 4.4 to 7.2) (Analysis 3.2).

The combination was significantly better than either sumatriptan or naproxen alone.

Headache relief at one hour

One study treating moderate to severe baseline pain provided data (Smith 2005); 73/250 participants experienced headache relief with combination therapy compared with 52/226 with sumatriptan alone, 67/248 with naproxen alone, and 29/241 with placebo. The data were insufficient for analysis.

Sustained pain-free during the 24 hours post dose

Sumatriptan plus naproxen versus placebo

Mild baseline pain

Eight studies (3396 attacks) provided data (Lipton 2009 Study 1; Lipton 2009 Study 2; Mannix 2009 Study 1; Mannix 2009 Study 2; Mathew 2009 Study 1; Mathew 2009 Study 2; Silberstein 2008 Study 1; Silberstein 2008 Study 2) for early use of the combined formulation, compared with placebo, when pain was still mild.

- The proportion of attacks with a 24-hour sustained pain-free response with sumatriptan plus naproxen 85/500 mg was 37% (741/2026; range 26% to 45%).
- The proportion of attacks with a 24-hour sustained pain-free response with placebo was 12% (166/1370; range 8% to 18%).
- The relative benefit of treatment compared with placebo was 3.0 (95% CI 2.6 to 3.6) (Analysis 1.3); the NNT was 4.1 (95% CI 3.7 to 4.6).

Calhoun 2014 reported a response rate of 69% with sumatriptan plus naproxen and 23% with placebo for this outcome in participants who experienced fewer than eight days/month with migraine headache or 15 days/month with migraine headache **or** neck pain.

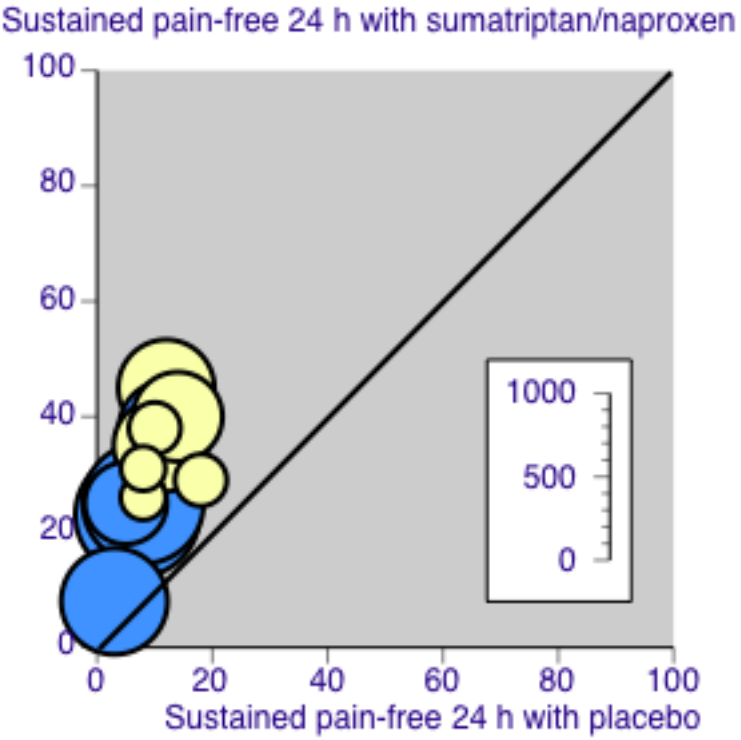
Moderate or severe baseline pain

Four studies (2596 attacks) provided data for use of either the combined formulation (Brandes 2007 Study 1; Brandes 2007 Study 2; TRX109011/13), or separate tablets (Smith 2005), compared with placebo, when pain was moderate or severe.

- The proportion of attacks with a 24-hour sustained pain-free response with sumatriptan plus naproxen 50 to 85/500 mg was 20% (262/1293; range 8.2% to 25%).
- The proportion of attacks with a 24-hour sustained pain-free response with placebo was 5.9% (77/1303; range 3.1% to 8.3%).
- The relative benefit of treatment compared with placebo was 3.4 (95% CI 2.7 to 4.4) (Analysis 1.3); the NNT was 7.0 (95% CI 5.9 to 8.5).
- For sumatriptan plus naproxen 85/500 mg alone (excluding the 50/500 mg dose) the NNT was 7.7 (95% CI 6.4 to 9.8), which was not significantly different from the NNT for the combined analysis.

Treating headache early, when pain was still mild, was significantly better than treating once pain was of moderate or severe intensity (z = 5.326; P value = 0.0001). A L'Abbé plot showed no evidence of heterogeneity between the studies, and there was considerable overlap between the two groups (Figure 7).

Figure 7. L'Abbé plot showing results for sumatriptan plus naproxen versus placebo for 24-hour sustained pain-free. Each circle represents a different study; blue circles are studies with moderate or severe baseline pain and cream circles are mild baseline pain; size of circle is proportional to size of study; diagonal is line of equivalence.



Sumatriptan plus naproxen versus sumatriptan or naproxen alone

Three studies provided data for use of either the combined formulation (Brandes 2007 Study 1; Brandes 2007 Study 2) or separate tablets (Smith 2005), compared with sumatriptan alone (1925 participants) or naproxen alone (1944 participants), when pain was moderate or severe.

- The proportion of participants with a 24-hour sustained pain-free response with sumatriptan plus naproxen 50 to 85/500 mg was 24% (236/976; range 23% to 25%).
- The proportion of participants with a 24-hour sustained pain-free response with sumatriptan alone was 14% (135/949; range 11% to 16%).
- The proportion of participants with a 24-hour sustained pain-free response with naproxen alone was 11% (104/968; range 10% to 12%).
- The relative benefit of the combination compared with sumatriptan alone was 1.7 (95% CI 1.4 to 2.1); the NNT was 10 (95% CI 7.4 to 15) (Analysis 2.3).
- The relative benefit of the combination compared with naproxen alone was 2.3 (95% CI 1.8 to 2.8); the NNT was 7.4 (95% CI 6.0 to 9.9) (Analysis 3.3).

The combination was significantly better than either sumatriptan or naproxen alone.

Sustained headache relief during the 24 hours post dose

Sumatriptan plus naproxen versus placebo

Four studies (2596 attacks) provided data for use of either the combined formulation (Brandes 2007 Study 1; Brandes 2007 Study 2; TRX109011/13), or separate tablets (Smith 2005), compared with placebo, when pain was moderate or severe.

- The proportion of attacks with 24-hour sustained headache relief with sumatriptan plus naproxen 50 to 85/500 mg was 43% (554/1293; range 34% to 48%).
- The proportion of attacks with 24-hour sustained headache relief with placebo was 16% (214/1303; range 14% to 18%).
- The relative benefit of treatment compared with placebo was 2.6 (95% CI 2.3 to 3.0) (Analysis 1.4); the NNT was 3.8 (95% CI 3.4 to 4.3).
- For sumatriptan plus naproxen 85/500 mg alone (excluding the 50/500 mg dose) the NNT was 3.9 (95% CI 3.4 to 4.5), which was not significantly different from the NNT for the combined analysis.

Sumatriptan plus naproxen versus sumatriptan or naproxen alone

Three studies provided data for use of either the combined formulation (Brandes 2007 Study 1; Brandes 2007 Study 2), or separate tablets (Smith 2005), compared with sumatriptan alone (1925 participants) or naproxen alone (1944 participants), when pain was moderate or severe.

- The proportion of participants with 24-hour sustained headache relief with sumatriptan plus naproxen 50 to 85/500 mg was 46% (447/976; range 44% to 48%).
- The proportion of participants with 24-hour sustained headache relief with sumatriptan alone was 33% (314/949; range 29% to 35%).
- The proportion of participants with 24-hour sustained headache relief with naproxen alone was 28% (271/968; range 25% to 30%).
- The relative benefit of the combination compared with sumatriptan alone was 1.4 (95% CI 1.2 to 1.6); the NNT was 7.9 (95% CI 5.9 to 12) (Analysis 2.4).
- The relative benefit of the combination compared with naproxen alone was 1.6 (95% CI 1.5 to 1.9); the NNT was 5.6 (95% CI 4.5 to 7.4) (Analysis 3.4).

The combination was significantly better than either sumatriptan or naproxen alone.

Summary of results: Pain-free and headache relief

	Baseline pain	Studies	Attacks treated	Treatment (%)	Placebo or comparator (%)	Risk ratio (95% CI)	NNT (95% CI)
Pain-free at 2 h							
Sumatriptan plus naproxen 85/500 mg vs placebo	mild	8	3395	50	18	2.8 (2.4 to 3.1)	3.1 (2.9 to 3.5)
Sumatriptan plus naproxen 50-85/500 mg vs placebo	≥ mod	4	2596	28	7.7	3.7 (3.0 to 4.5)	4.9 (4.3 to 5.7)
Sumatriptan plus naproxen 85/500 mg vs placebo	≥ mod	3	2105	27	8.1	3.3 (2.6 to 4.1)	5.4 (4.6 to 6.5)
Sumatriptan plus naproxen 50-85/500 mg vs sumatriptan 50-85 mg	≥ mod	3	1925	32	23	1.4 (1.2 to 1.7)	10 (7.4 to 18)
Sumatriptan plus naproxen 50-85/500 mg vs naproxen 500 mg	≥ mod	3	1944	32	16	2.0 (1.7 to 2.4)	6.1 (5.0 to 7.9)
Headache relief at 2 h							
Sumatriptan plus naproxen 50-85/500 mg vs placebo	≥ mod	4	2596	58	27	2.2 (2.0 to 2.4)	3.2 (2.9 to 3.6)
Sumatriptan plus naproxen 85/500 mg vs placebo	≥ mod	3	2105	57	27	2.1 (1.9	3.4 (3.0

						to 2.4)	to 3.9)
Sumatriptan plus naproxen 50-85/500 mg vs sumatriptan 50-85 mg	≥ mod	3	1925	62	52	1.2 (1.1 to 1.3)	9.8 (6.8 to 17)
Sumatriptan plus naproxen 50-85/500 mg vs naproxen 500 mg	≥ mod	3	1944	62	44	1.4 (1.3 to 1.5)	5.5 (4.4 to 7.2)
Sustained pain-free during the 24 h post dose							
Sumatriptan plus naproxen 85/500 mg vs placebo	mild	8	3396	37	12	3.0 (2.6 to 3.6)	4.1 (3.7 to 4.6)
Sumatriptan plus naproxen 50-85/500 mg vs placebo	≥ mod	4	2596	20	6	3.4 (2.7 to 4.4)	7.0 (5.9 to 8.5)
Sumatriptan plus naproxen 85/500 mg vs placebo	≥ mod	3	2005	19	6	3.1 (2.4 to 4.0)	7.7 (6.4 to 9.8)
Sumatriptan plus naproxen 50-85/500 mg vs sumatriptan 50-85 mg	≥ mod	3	1925	24	14	1.7 (1.4 to 2.1)	10 (7.4 to 15)
Sumatriptan plus naproxen 50-85/500 mg vs naproxen 500 mg	≥ mod	3	1944	24	11	2.3 (1.8 to 2.8)	7.4 (6.0 to 9.9)
Sustained headache relief during the 24 h post dose							
Sumatriptan plus naproxen 50-85/500 mg vs placebo	≥ mod	4	2596	43	16	2.6 (2.3	3.8 (3.4

						to 3.0)	to 4.3)
Sumatriptan plus naproxen 85/500 mg vs placebo	≥ mod	3	2107	42	16	2.6 (2.2 to 3.0)	3.9 (3.4 to 4.5)
Sumatriptan plus naproxen 50-85/500 mg vs sumatriptan 50-85 mg	≥ mod	3	1925	46	33	1.4 (1.2 to 1.6)	7.9 (5.9 to 12)
Sumatriptan plus naproxen 50-85/500 mg vs naproxen 500 mg	≥ mod	3	1944	46	28	1.6 (1.5 to 1.9)	5.6 (4.5 to 7.4)

Subgroup analysis of primary outcomes

Subgroup analysis according to the timing of initial medication (early while pain was mild, or once pain was moderate or severe) has been considered in the main analysis above, with early treatment giving better efficacy for pain-free responses at two hours and during the 24 hours post dose. Similarly, dose has been considered in the main analysis: all studies used sumatriptan 85 mg combined with naproxen 500 mg except Smith 2005, which used sumatriptan 50 mg combined with naproxen 500 mg. Inclusion of the lower 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. There was no evidence that results from the studies reporting combined data from both phases of the cross-over differed from those reporting first-phase-only data (Mathew 2009 Study 1; Mathew 2009 Study 2; TRX109011/13). There was also no evidence that results for the study that enrolled only participants who had previously had a poor response to triptans with a short half-life (including sumatriptan) differed from those who enrolled participants who had previously tolerated treatment with a triptan or had no contraindications, or both (Mathew 2009 Study 1; Mathew 2009 Study 2).

Two studies included only participants with menstrual migraine (Mannix 2009 Study 1; Mannix 2009 Study 2). Results for these studies were similar to other studies treating mild pain for the outcomes of pain-free at two hours (Figure 3), and sustained pain-free during the 24 hours post dose (Analysis 1.3); removing the menstrual migraine studies from the analyses made no difference.

The three cross-over studies that did not report first-period data separately, but only all-period data (Mathew 2009 Study 1; Mathew 2009 Study 2; TRX109011/13), gave results that were indistinguishable from those from other studies (Figure 3; Figure 5; Analysis 1.3; Analysis 1.4).

Sumatriptan plus naproxen versus active controls

One study compared the combination with a butalbital-containing active comparator (TRX109011/13); there were insufficient data for a head-to-head analysis of the two treatments from this single trial. Sumatriptan plus naproxen was reported to be statistically superior to the butalbital combination for pain-free response at all time points between 2 and 48 hours.

Adverse events

Any adverse event

All studies reported some information about participants who experienced one or more adverse events, but the reporting was inconsistent. Mannix 2009 Study 1 and Mannix 2009 Study 2 reported only that less than a certain percentage had experienced drug-related adverse events. Cross-over studies (Mathew 2009 Study 1 and Mathew 2009 Study 2) reported the percentage with adverse events for each treatment; the reported safety populations for the two studies were 144 and 139 participants, respectively; for the analysis, we have assumed that all took both study medications. The other studies reported participants with adverse events in each treatment arm, but Brandes 2007 Study 1, Brandes 2007 Study 2, and Smith 2005 reported events occurring within 24 hours of taking study medication, while Lipton 2009 Study 1, Lipton 2009 Study 2, and TRX109011/13 reported over 72 hours, and Silberstein 2008 Study 1 and Silberstein 2008 Study 2 up to one week. 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 different time periods for analysis.

Sumatriptan plus naproxen 85/500 mg versus placebo

Six studies (2823 attacks) treating when pain was still mild (Lipton 2009 Study 1; Lipton 2009 Study 2; Mathew 2009 Study 1; Mathew 2009 Study 2; Silberstein 2008 Study 1; Silberstein 2008 Study 2), and four (2793 attacks) treating when pain was moderate or severe (Brandes 2007 Study 1; Brandes 2007 Study 2; Smith 2005; TRX109011/13), provided data for analysis.

Mild baseline pain

- The proportion of attacks with one or more adverse events with sumatriptan plus naproxen 85/500 mg was 14% (241/1749; range 9.4% to 19%).
- The proportion of attacks with one or more adverse events with placebo was 8.2% (88/1074; range 4.2% to 14%).
- The RR of treatment compared with placebo was 1.5 (95% CI 1.2 to 1.9) (Analysis 1.5); the NNH was 18 (95% CI 13 to 30).

Moderate to severe baseline pain

- The proportion of attacks with one or more adverse events with sumatriptan plus naproxen 85/500 mg was 21% (291/1394; range 8.9% to 27%).
- The proportion of attacks with one or more adverse events with placebo was 11% (148/1399; range 6.9% to 15%).
- The RR of treatment compared with placebo was 2.0 (95% CI 1.6 to 2.4) (Analysis 1.5); the NNH was 9.7 (95% CI 7.7 to 13).

There was a significant difference in the number of attacks in which one or more adverse events was experienced between those treated early when pain was still mild, and those treated when pain was moderate or severe (z = 2.6167, P value = 0.0088).

Sumatriptan plus naproxen 50 to 85/500 mg versus sumatriptan alone or naproxen alone

Three studies provided data comparing sumatriptan/naproxen versus both sumatriptan (1952 participants) and naproxen (1970 participants) alone (Brandes 2007 Study 1; Brandes 2007 Study 2; Smith 2005). Medication was taken when PI was moderate or severe.

- The proportion of participants experiencing adverse events with sumatriptan/naproxen 85/500 mg was 26% (255/988; range 23% to 27%).
- The proportion of participants experiencing adverse events with sumatriptan 85 mg alone was 26% (249/964; range 24% to 28%).
- The proportion of participants experiencing adverse events with naproxen 500 mg alone was 15% (143/982; range 13% to 17%).

- The RR of the combination compared with sumatriptan alone was 1.0 (95% CI 0.9 to 1.2) (Analysis 2.5); the NNH was not calculated.
- The RR of the combination compared with naproxen alone was 1.8 (95% CI 1.5 to 2.1); the NNH was 8.9 (95% CI 6.8 to 13) (Analysis 3.5).

There was no difference in these studies between the combination and sumatriptan alone, but fewer participants experienced adverse events with naproxen alone.

Specific adverse events

Dizziness, paraesthesia, somnolence, nausea, dyspepsia, dry mouth, and chest discomfort were the most commonly reported adverse events, and were somewhat more common with combination therapy than monotherapy, and more common with active therapies than placebo. The incidence of any specific event in individual studies was low (less than 4%) and not consistently reported across studies, so numbers of reported events were small and no analysis was possible.

Serious adverse events

One participant, who had several cardiovascular risk factors, experienced heart palpitations and was admitted to hospital after receiving sumatriptan 85 mg; the event was judged probably related to study medication (Brandes 2007 Study 1). Seven participants in Lipton 2009 Study 1 and Lipton 2009 Study 2 experienced serious adverse events, none of which were judged related to study medication or occurred within 72 hours of receiving study medication. A further five serious adverse events occurred in TRX109011/13, which were also judged unrelated to the study medication.

Withdrawals

Six studies reported that there were no adverse event withdrawals (Brandes 2007 Study 1; Mannix 2009 Study 1; Mannix 2009 Study 2; Mathew 2009 Study 2; Silberstein 2008 Study 1; Silberstein 2008 Study 2), and another did not mention any adverse event withdrawals (Smith 2005). There was one withdrawal (palpitations following sumatriptan 85 mg) in Brandes 2007 Study 1; eight withdrawals (all following combination treatment, three with mild or moderate chest discomfort) in Lipton 2009 Study 1; six withdrawals (three with mild or moderate chest discomfort and three with nausea following combination treatment, and one with nausea following placebo) in Lipton 2009 Study 2; and one (muscle tightness, heaviness, anxiety, and nervousness following placebo) in Mathew 2009 Study 1. Four subjects were withdrawn in TRX109011/13; two due to pregnancy, one due to use of prohibited medication, and one due to a new diagnosis of breast cancer.

Participants who took rescue medication were classified as withdrawals due to lack of efficacy, and details are reported under 'Use of rescue medication' (Appendix 8).

Exclusion of participants from analyses after randomisation were mostly due to protocol violations or failing to take the medication (no qualifying headache, or cross-over not completed), and were generally well reported. Numbers of participants lost to follow-up, or withdrawing due for unspecified reasons were small and unlikely to influence results.

Other outcomes

Results for use of rescue medication, relief of headache-associated symptoms, and relief of functional disability are in Appendix 8.

DISCUSSION

Summary of main results

This updated review included 13 randomised, double-blind, placebo-controlled studies, of which 12 contributed to analyses. For the primary outcome of pain-free at two hours, data were available for analysis for 3318 headaches treated with sumatriptan plus naproxen and 2673 treated with placebo. Of these, 2025 headaches were treated when the pain was of mild severity and 1293 when the pain was moderate or severe. This allowed analysis of the effect of different dosing regimens on the primary outcomes. Most studies used a standard combination tablet of sumatriptan 85 mg and naproxen 500 mg, but one used two separate tablets of sumatriptan 50 mg and naproxen 500 mg. Two studies included active comparators, which allowed analysis of the combination formulation versus monotherapy, for example, sumatriptan or naproxen. One study included a different active comparator, but there were insufficient data for analysis (TRX109011/13).

For the IHS preferred outcome of pain-free at two hours, the combination formulation was better than placebo both when pain was mild at baseline and when it was moderate to severe. NNTs were 3.1 and 4.9, with 50% and 28% of people being pain-free with mild or moderate to severe pain, respectively (high quality evidence). A greater response was seen when headaches were mild and this result was statistically significant (P value < 0.0001). For headache relief at two hours (analysis possible only for headaches with initial intensity of moderate or severe), the combination was better than placebo. The NNT was 3.2, with 58% of participants responding compared with 27% with placebo (high quality evidence).

For the IHS preferred outcome of sustained pain-free during the 24 hours post dose, the combination formulation was better than placebo both when pain was mild at baseline and when it was moderate to severe. NNTs were 4.1 and 7.0, with 37% and 20% of people being pain free with the combination, compared with 12% and 6% with placebo, for mild and moderate to severe pain, respectively (high and moderate quality evidence). A greater response was seen when headaches were mild and this result was statistically significant (P value < 0.0008). For sustained headache relief during the 24 hours post dose, combination was better than placebo, with an NNT of 3.8 and 43% of participants responding compared with 16% with placebo (high quality evidence). Modest success rates for levels of PR considered useful by patients is the rule with different analgesics across many acute and chronic pain conditions (Moore 2013).

One study did not contribute to analyses because of uncertainty about the denominator used to calculate the reported response rates (Calhoun 2014). This study recruited a slightly different population, requiring that participants experienced fewer than 8 migraine headaches per month or fewer than 15 days per month with either headache or neck pain in any of the 3 months before screening. The authors believe that neck pain is integrally related to migraine, and that by ignoring it, studies recruit people who are not "truly episodic migraineurs". Their results suggest somewhat

higher response rates in both sumatriptan plus naproxen and placebo treatment arms for pain-free at two hours, and for 24-hour sustained pain freedom. They also report a more rapid response than seen in earlier studies (5% pain-free at 15 minutes with sumatriptan plus naproxen, 0% with placebo; 43 participants). Making various assumptions about the denominator to allow inclusion of this study in the analysis did not significantly change the results. This was unsurprising because of the small size of the study. The authors' hypothesis that this population of migraineurs achieve better response rates remains to be tested in larger studies.

In all efficacy analyses, combination treatment was superior to monotherapy with either sumatriptan or naproxen alone. The use of separate tablets using sumatriptan in a lower dose (50 mg versus 85 mg) did not affect any results in a meaningful way.

No analysis was possible for times shorter than two hours. Overall, 58% of participants treated with combination experienced headache relief at two hours, and just under 43% sustained relief for 24 hours. Half of the participants were pain free at two hours when treated early (mild pain), but only 28% when treated when pain was moderate or severe. For sustained pain-free during the 24 hours post dose the percentages were lower, at 37% for mild pain and 20% for moderate or severe pain.

There was a significant difference in the number of participants experiencing one or more adverse events between those treating early when pain was still mild (NNH 18) and those treating when pain was moderate or severe (NNH 9.7) (moderate quality evidence). Most adverse events were described as mild or moderate, and transient. The incidence of any specific adverse event was low (< 4%) and serious adverse events and adverse event withdrawals were uncommon.

Additional analyses showed that combination was significantly better than placebo or either drug alone for relief of associated symptoms (nausea, photophobia, and phonophobia) and functional disability (Appendix 8).

Overall completeness and applicability of evidence

Included participants all had a diagnosis of migraine headaches according to IHS criteria and the information for active comparators was sufficiently large to allow for comparisons with placebo and both sumatriptan and naproxen monotherapy in order to generate conclusions about relative efficacy and harm. Most participants were recruited from neurology outpatient departments, 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. Additionally, two studies specifically recruited participants who had not previously experienced relief with short-acting triptans, including sumatriptan, and all studies excluded individuals who experience chronic migraine or very frequent migraines (more than six or eight attacks per month), so results may not be applicable to those with frequent attacks. These factors could lead to an underestimate of treatment effect. All studies included participants with or without aura, but none reported results for the two types separately.

A study of sumatriptan plus naproxen in people with probable migraine (ie who satisfy all but one of the diagnostic criteria for migraine (IHS 2004)) found similar benefits, compared with placebo, to those found in people who satisfy the strict diagnostic criteria for migraine (TRX107563 and Silberstein et al. 2014). This is important because probable migraine is common amongst people seeking treatment for headache.

Individual studies are underpowered to determine differences between treatments for adverse events, and even pooling studies may not provide adequate numbers of events to demonstrate differences or allow confidence in the size of the effect. Single-dose studies are certainly unlikely to reveal rare, but potentially serious, adverse events. In these studies, the number of participants experiencing any adverse event with active treatment was greater than with placebo. 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.

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 the primary outcomes we sought.

We considered no studies to be at high risk of bias for any of the criteria evaluated, except for Calhoun 2014, which had fewer than 50 participants per treatment arm, but did not contribute to any analyses.

We judged the overall quality of the evidence as moderate to high for comparisons of sumatriptan plus naproxen with placebo, and moderate for comparisons of the combination with the individual components. Quality was downgraded because of the modest number of studies, and for some comparisons events, which meant that further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Potential biases in the review process

One potential area of concern is the small numbers of events for some outcomes, particularly for specific adverse events.

For three of the cross-over studies (Mathew 2009 Study 1; Mathew 2009 Study 2; TRX109011/13), we have used data from all phases. While this may introduce unknown biases (Elbourne 2002), the data from these studies was entirely consistent with data from all others for efficacy outcomes.

We identified a large amount of data in comparisons with placebo. Approximately 2000 additional participants would have to have been involved in unpublished trials with zero treatment effect for the NNT for headache relief at two hours to increase above 6 (which we considered the limit of clinical utility in this situation) with the combination therapy (Moore 2008). This equates to five studies with over 400 participants in active and placebo treatment arms. Similarly, over 5000 additional participants would have to have been involved in unpublished trials with zero treatment effects for the NNT for pain-free at two hours to increase above 8 (considered to be the limit of clinical utility in this situation), when baseline pain was mild, or almost 2000 when baseline pain was moderate or

severe. It is unlikely that such a large amount of unidentified data exists, so publication bias is not a concern.

Agreements and disagreements with other studies or reviews

Naproxen for acute migraine is the subject of two systematic reviews (Bandolier 2000; Law 2013b). One Cochrane review provides information on oral sumatriptan alone (Derry 2012). NNT values for headache relief at two hours were:

Drug and dose (mg)	NNT for headache relief at 2 h
Naproxen 500 mg vs placebo	6.2
Sumatriptan 50 mg vs placebo	4.0
Sumatriptan 100 mg vs placebo	3.5
Sumatriptan 50-85 mg plus naproxen 500 mg vs placebo	3.2

The results, for this outcome, of the sumatriptan plus naproxen combination show the additivity of pain-relieving drugs demonstrated in several acute pain conditions including migraine (Moore 2012). The combination produced lower (better) NNT values versus placebo for the outcome of headache relief at two hours than did sumatriptan or naproxen alone. Adverse event experiences were similar for sumatriptan alone and in combination.

Suthisisang 2011 is a meta-analysis of three of the 12 studies included in this review (Brandes 2007 Study 1; Brandes 2007 Study 2; Smith 2005). The meta-analysis quotes NNT values for sumatriptan plus naproxen versus sumatriptan monotherapy of 10 (95% CI 8 to 17) for pain-free at two hours, 10 (8 to 15) for sustained pain-free during the 24 hours post dose, 10 (7 to 17) for headache relief at two hours, and 8 (6 to 13) for sustained headache relief during the 24 hours post dose. These are the only studies that allow comparisons between the combination and sumatriptan monotherapy, and the results from the meta-analysis in Suthisisang 2011 are consistent with the results reported in this review for the same comparison with the same studies.

Khoury 2010 reviewed various aspects of the combination therapy including mode of action, pharmacokinetics, and efficacy, but no data synthesis was carried out. A combined analysis of two randomised studies reported on the composite endpoint of sustained pain-free with no adverse events (Landy 2009); this showed that with a composite endpoint sumatriptan plus naproxen was significantly better than placebo or either component alone.

A randomised, double-blind, active-controlled trial using the combination treatment and the individual monotherapies looked at the primary endpoint of changes in blood pressure from baseline over a six-month period (White 2011), but with no efficacy or adverse event data relating to single migraine episodes. This showed no clinically significant blood pressure changes, and also allowed some analysis of longer-term adverse events. In particular, the study showed that the type of adverse events were broadly similar over this longer time scale, and that the proportions of adverse events with each therapy (20%, 29%, and 18% for combination, sumatriptan alone, and naproxen alone, respectively) in White 2011 were equivalent to those seen here in single-episode analyses (21%, 26%, and 15% for combination, sumatriptan alone, and naproxen alone, respectively, in participants with moderate to severe baseline pain).

AUTHORS' CONCLUSIONS

Implications for practice

For people with migraine

The combination of sumatriptan plus naproxen is better than naproxen alone, and probably better than sumatriptan alone. It is not clear whether there is any clinical significance to the benefits observed with the combination over sumatriptan alone. More people get good relief when medication is taken early in the attack, when pain is still mild. Adverse events are more common with the combination and sumatriptan alone than with placebo or naproxen alone, but these events do not usually stop people from taking the medicine.

The combination tablet is not available in most countries, but the individual components are widely available and can be taken together.

For clinicians

The combination of sumatriptan plus naproxen provides good levels of relief to more people than either drug alone, but the clinical significance of the benefits observed with the combination over sumatriptan alone are unclear. More people get good relief when medication is taken early in the attack, when pain is still mild, so early treatment should be encouraged. Adverse events are more common with the combination and sumatriptan alone than with placebo or naproxen alone, but these events rarely led to withdrawal in these studies.

The combination tablet is not available in many countries outside the US, but the components as separate tablets can be taken simultaneously, although sumatriptan alone is available only in 50

and 100 mg doses. The included study using separate tablets used the 50 mg dose.

For policy makers

No single treatment provides a good response in all people with migraine. Combining two drugs with different actions is a rational option to increase the number who benefit, and the combination of sumatriptan with naproxen does provide good outcomes to more people than either drug alone, without compromising tolerability, although the benefits over sumatriptan alone are small. As with monotherapy, early treatment with this combination gives better results and should be promoted.

The combination tablet is not available in most countries outside the US, but the components as separate tablets can be taken simultaneously, although sumatriptan alone is available only in 50 and 100 mg doses. The included study using separate tablets used the 50 mg dose.

For funders

The combination of sumatriptan with naproxen provides good outcomes to more people than either drug alone, without compromising tolerability, although the benefits over sumatriptan alone are small. The combination tablet is not available in many countries outside the US, but the components as separate tablets can be taken simultaneously, although sumatriptan alone is available only in 50 and 100 mg doses. The included study using separate tablets used the 50 mg dose. Using separate tablets may be less convenient, but is considerably less costly.

Implications for research

General

Migraine is common and debilitating. Combining two drugs with different modes of action to treat migraine offers the opportunity to target different components of migraine pathophysiology. It may also be possible to achieve a good response with lower doses of one or both drugs.

These studies combining sumatriptan with naproxen demonstrate better results than either drug alone, but studies are needed to determine which triptan and which NSAID make the best combination, and for whom. To date there are few published trials of different combinations. Naproxen 500 mg is of limited efficacy when used as a monotherapy in migraine when pain is moderate or severe. Ibuprofen 400 mg and diclofenac 50 mg produce lower (better) NNTs, and may be more appropriate nonsteroidal anti-inflammatory drugs to be used in combination with a triptan.

Including a broader spectrum of people with migraine-like headaches, some of whom may not fulfil IHS criteria for migraine, could increase the generalisability of study results, and help to identify subpopulations who respond differently.

Design

The design of the trials is good, and major changes appear unnecessary.

Measurement (endpoints)

Clinically useful outcomes in migraine trials are well established, but part of the reason for investigating drug combinations is to achieve earlier responses and to reduce recurrence of the headache, which is not uncommon. This requires both routine measurement and reporting of outcomes at earlier (eg at half- and one-hour) and later (eg at 24- and 48-hour) time points.

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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 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 to 65 years. History: > 6 months with frequency of 2 to 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 plus 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)

Brandes 2007 Study 1 *(Continued)*

	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 AEs 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 (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs described
Study size	Low risk	> 200 participants per treatment arm

Brandes 2007 Study 2

Study characteristics

Methods	Multicentre, R, DB, PC, parallel group. Single dose to treat 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 to 65 years. History: > 6 months with frequency of 2 to 6 per month and untreated severity ≥ moderate Excluded: uncontrolled hypertension, cardio- or cerebrovascular disease, using MAOI, ergot, SJW, or NSAID

Brandes 2007 Study 2 *(Continued)*

	N = 1495 F = 88% Mean age 40 years 76% without aura
Interventions	Sumatriptan 85 mg plus 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 AEs 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 (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs described
Study size	Low risk	> 200 participants per treatment arm

Calhoun 2014

Study characteristics	
Methods	Single centre, R, DB, PC, cross-over study 4 non-menstrual migraines treated with single dose of study medication (4 sumatriptan plus naproxen, 1 placebo, in random order), within 30 min of onset of headache or neck pain, and only if preceding day was free of both headache and neck pain
Participants	Episodic migraine ± aura (IHS 2004), aged 18 to 55 years. 1-year history, with 2 to 7 attacks per month in previous 3 months, able to recognise in mild pain stage. Preventive medication stable for previous 2 months and throughout study Excluded: ≥ 8 migraine attacks per month or > 15 days per month of headache or neck pain, uncontrolled hypertension, cardio- or cerebrovascular disease, peripheral vascular disease, using MAOI, ergot, SJW N = 43 F = 95% Mean age 36 years
Interventions	Sumatriptan 85 mg plus naproxen 500 mg, n = 43 Placebo n = 43 Rescue medication allowed with open label sumatriptan plus naproxen or other approved medication after 2 h for inadequate response
Outcomes	Pain-free at 2 h 24-h sustained pain-free Adverse events
Notes	Oxford Quality Score: R2, DB1, W0. Total = 3 Authors were contacted to find out what denominator was used to calculate response rate, but the information was not provided

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Study drug and placebo were dispensed based on a randomization code"
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Method to maintain blinding not described: "blister pack containing 4 pills", but unclear if pills were identical
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Results reported for ITT population, but it was unclear whether the denominator used to calculate per cent response was participants or headache episodes (each participant was asked to treat 4 episodes)
Study size	High risk	< 50 participants per treatment arm

Lipton 2009 Study 1

Study characteristics	
Methods	Multicentre, R, DB, PC, cross-over. Single dose per attack. 4 attacks treated: all with active or 3 active and 1 placebo (in random order). Washout between attacks not specified, but all headache medications prohibited within 24 h of a treated attack, and AE data collected for 72 h after treatment Medication taken within 1 h of onset when PI was mild Assessments at 0, 2, 4, 24 h
Participants	Migraine ± aura (IHS 2004), aged 18 to 65 years. History ≥ 6 months with frequency of 2 to 6 attacks per month and untreated severity ≥ moderate and identifiable mild phase Excluded: uncontrolled hypertension, cardio- or cerebrovascular disease N = 570 (568 for efficacy) F = 89% Mean age 42 years
Interventions	Sumatriptan plus naproxen 85/500 mg (1693 attacks treated) Placebo (424 attacks treated) 5 treatment groups with different medication sequences (Nap: naproxen; P: placebo; Sum: sumatriptan) P, Sum/Nap, Sum/Nap, Sum/Nap; Sum/Nap, P, Sum/Nap, Sum/Nap; Sum/Nap, Sum/Nap, P, Sum/Nap; Sum/Nap, Sum/Nap, Sum/Nap, P; Sum/Nap, Sum/Nap, Sum/Nap, Sum/Nap Rescue medication allowed after 2 h if necessary (recommended 2 x 220 mg naproxen sodium with additional 1 x 220 mg 6 h later if needed)
Outcomes	Pain-free at 2 h 24-h sustained pain-free Presence and relief of associated symptoms at 2 h Use of rescue medication AEs 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 (performance bias and detection bias) All outcomes	Unclear risk	Not described

Lipton 2009 Study 1 *(Continued)*

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

Lipton 2009 Study 2

Study characteristics	
Methods	Multicentre, R, DB, PC, cross-over. Single dose per attack. 4 attacks treated: all with active or 3 active and 1 placebo (in random order). Washout between attacks not specified, but all headache medications prohibited within 24 h of a treated attack, and AE data collected for 72 h after treatment Medication taken within 1 h of onset when PI was mild Assessments at 0, 2, 4, 24 h
Participants	Migraine ± aura (IHS 2004), aged 18 to 65 years. History ≥ 6 months with frequency of 2 to 6 attacks per month and untreated severity ≥ moderate and identifiable mild phase Excluded: uncontrolled hypertension, cardio- or cerebrovascular disease N = 565 (563 for efficacy) F = 90% Mean age 41 years
Interventions	Sumatriptan plus naproxen 85/500 mg (1678 attacks treated) Placebo (422 attacks treated) 5 treatment groups with different medication sequences (Nap: naproxen; P: placebo; Sum: sumatriptan) P, Sum/Nap, Sum/Nap, Sum/Nap; Sum/Nap, P, Sum/Nap, Sum/Nap; Sum/Nap, Sum/Nap, P, Sum/Nap; Sum/Nap, Sum/Nap, Sum/Nap, P; Sum/Nap, Sum/Nap, Sum/Nap, Sum/Nap Rescue medication allowed after 2 h if necessary (recommended 2 x 220 mg naproxen sodium with additional 1 x 220 mg 6 h later if needed)
Outcomes	Pain-free at 2 h 24-h sustained pain-free Presence and relief of associated symptoms at 2 h Use of rescue medication AEs Withdrawals
Notes	Oxford Quality Score: R1, DB1, W1. Total = 3

Risk of bias

Bias	Authors' judgement	Support for judgement

Lipton 2009 Study 2 *(Continued)*

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

Mannix 2009 Study 1

Study characteristics	
Methods	Multicentre, R, DB, PC, parallel group. Single dose to treat single attack Medication taken when PI mild and within 1 h of onset Assessments at 0, 0.5, 1, 1.5, 2, 4, 24, 48 h
Participants	Migraine ± aura (IHS 2004), aged ≥ 18 years. History: frequency of migraines 1 to 6 per month with menstrual migraine in 2/3 previous cycles and dysmenorrhoea in 2/3 cycles. Untreated severity ≥ moderate, with identifiable mild phase N = 312 (311 for efficacy) F = 100% Mean age 37 years Aura: 26%; primary dysmenorrhoea: 77%
Interventions	Sumatriptan 85 mg plus naproxen 500 mg, n = 152 Placebo, n = 160 Rescue medication allowed after 2 h if necessary (including second dose, sumatriptan or naproxen sodium)
Outcomes	Pain-free at 2 h 24-h sustained pain-free Use of rescue medication up to 48 h AEs Withdrawals
Notes	Oxford Quality Score: R2, DB1, W1. Total = 4
Risk of bias	

Mannix 2009 Study 1 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomly assigned by a computer generated code"
Allocation concealment (selection bias)	Low risk	Remote allocation (computerised registration and ordering system)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs described
Study size	Unclear risk	50 to 200 participants per treatment arm

Mannix 2009 Study 2

Study characteristics	
Methods	Multicentre, R, DB, PC, parallel group. Single dose to treat single attack Medication taken when PI mild and within 1 h of onset Assessments at 0, 0.5, 1, 1.5, 2, 4, 24, 48 h
Participants	Migraine ± aura (IHS 2004), aged ≥ 18 years. History: frequency of migraines 1 to 6 per month with menstrual migraine in 2/3 previous cycles and dysmenorrhoea in 2/3 cycles. Untreated severity ≥ moderate, with identifiable mild phase N = 311 (310 for efficacy) F = 100% Mean age 37 years Aura: 40%; primary dysmenorrhoea: 92%
Interventions	Sumatriptan 85 mg plus naproxen 500 mg, n = 151 Placebo, n = 160 Rescue medication allowed after 2 h if necessary (including second dose, sumatriptan or naproxen sodium)
Outcomes	Pain-free at 2 h 24-h sustained pain-free Use of rescue medication up to 48 h AEs Withdrawals
Notes	Oxford Quality Score: R2, DB1, W1. Total = 4

Mannix 2009 Study 2 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomly assigned by a computer generated code"
Allocation concealment (selection bias)	Low risk	Remote allocation (computerised registration and ordering system)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs described
Study size	Unclear risk	50 to 200 participants per treatment arm

Mathew 2009 Study 1

Study characteristics	
Methods	Multicentre, R, DB, PC, cross-over. Single dose to treat single attack. Washout between attacks ≥ 1 week Medication taken when PI mild and within 1 h of onset Assessments at 0, 0.5, 1, 1.5, 2, 4, 24, 48 h
Participants	Migraine ± aura (IHS 2004), aged 18 to 65 years, poor response to triptans with short half-life. History: frequency of 1 to 8 per month, < 15 headache days monthly. Untreated severity ≥ mild Excluded: uncontrolled hypertension, cardio- or cerebrovascular disease N = 144 (139 for efficacy) F = 85% Mean age 41 years Aura: 32%
Interventions	Sumatriptan 85 mg plus naproxen 500 mg, n = 136 Placebo, n = 134 Rescue medication allowed after 2 h if necessary (not specified)
Outcomes	Pain-free at 2 h 24-h sustained pain-free Presence and relief of associated symptoms at 2 h Use of rescue medication AEs

Mathew 2009 Study 1 *(Continued)*

	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 (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs described
Study size	Unclear risk	50 to 200 participants per treatment arm

Mathew 2009 Study 2

Study characteristics	
Methods	Multicentre, R, DB, PC, cross-over. Single dose to treat single attack. Washout between attacks ≥ 1 week Medication taken when PI mild and within 1 h of onset Assessments at 0, 0.5, 1, 1.5, 2, 4, 24, 48 h
Participants	Migraine ± aura (IHS 2004), aged 18 to 65 years, poor response to triptans with short half-life. History: frequency of 1 to 8 per month, < 15 headache days monthly. Untreated severity ≥ mild Excluded: uncontrolled hypertension, cardio- or cerebrovascular disease N = 137 (131 for efficacy) F = 93% Mean age 40 years 27% without aura
Interventions	Sumatriptan 85 mg plus naproxen 500 mg, n = 134 Placebo, n = 133 Rescue medication allowed after 2 h if necessary (not specified)
Outcomes	Pain-free at 2 h 24-h sustained pain-free Presence and relief of associated symptoms at 2 h

Mathew 2009 Study 2 *(Continued)*

	Use of rescue medication AEs 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 (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs described
Study size	Unclear risk	50 to 200 participants per treatment arm

Silberstein 2008 Study 1

Study characteristics	
Methods	Multicentre, R, DB, PC, parallel group. Single dose to treat single attack Medication taken when PI mild and within 1 h of onset Assessments at 0, 0.5, 1, 2, 4, 24 h
Participants	Migraine ± aura (IHS 2004), aged 18 to 65 years. History: ≥ 6 months with frequency of 2 to 6 attacks per month, and ≤ 15 per month. Untreated severity ≥ moderate, with identifiable mild pain phase Excluded: uncontrolled hypertension, cardio- or cerebrovascular disease, gastrointestinal history N = 580 (576 for efficacy) F = 87.5% Mean age 40 years Aura: 20%
Interventions	Sumatriptan 85 mg plus naproxen 500 mg, n = 283 Placebo, n = 297 Rescue medication allowed after 2 h if necessary (not triptans, NSAID-containing, ergot-containing or ergot-like medication)
Outcomes	Pain-free at 2 h

Silberstein 2008 Study 1 *(Continued)*

	24-h sustained pain-free Presence and relief of associated symptoms at 2 h Presence and relief of functional disability at 2 h (from Taylor 2007) Use of rescue medication AEs Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5

Risk of bias

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

Silberstein 2008 Study 2

Study characteristics	
Methods	Multicentre, R, DB, PC, parallel group. Single dose to treat single attack Medication taken when PI mild and within 1 h of onset Assessments at 0, 0.5, 1, 2, 4, 24 h
Participants	Migraine ± aura (IHS 2004), aged 18 to 65 years. History: ≥ 6 months with frequency of 2 to 6 attacks per month, and ≤ 15 per month. Untreated severity ≥ moderate, with identifiable mild pain phase Excluded: uncontrolled hypertension, cardio- or cerebrovascular disease, gastrointestinal history N = 542 (535 for efficacy) F = 90.5% Mean age 41 years 66% without aura
Interventions	Sumatriptan 85 mg plus naproxen 500 mg, n = 278 Placebo, n = 264

Silberstein 2008 Study 2 *(Continued)*

	Rescue medication allowed after 2 h if necessary (not triptans, NSAID-containing, ergot-containing or ergot-like medication)
Outcomes	Pain-free at 2 h 24-h sustained pain-free Presence and relief of associated symptoms at 2 h Presence and relief of functional disability at 2 h (from Taylor 2007) Use of rescue medication AEs Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5

Risk of bias

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

Smith 2005

Study characteristics

Methods	Multicentre, R, DB, DD, parallel group. Single dose to treat 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 to 6 attacks per month, and able to tolerate oral triptan or ergot derivative N = 972 F = 91% Mean age 42 years Without aura: > 70%

Smith 2005 *(Continued)*

Interventions	Sumatriptan 50 mg plus 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 AEs Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	DD method, with sumatriptan encapsulated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs described
Study size	Low risk	> 200 participants per treatment arm

TRX109011/13

Study characteristics

Methods	Multicentre, R, DB, DD, 3 phase cross-over. Single dose of each medication to treat single attack. Washout between attacks ≥ 72 h Medication taken when pain ≥ moderate

TRX109011/13 *(Continued)*

	Assessments at 0, 2, 4, 6, 8, 24, 48 h
Participants	Migraine ± aura (IHS 2004), aged ≥ 18 years. History of 2 to 8 attacks per month in previous 3 months N = 375 attacks (ITT; 442 attacks for safety) F = 88% Mean age 43 years
Interventions	Sumatriptan 50 mg plus naproxen 500 mg, n = 406 (317 for efficacy) Paracetamol (acetaminophen) 325 mg + caffeine 40 mg + butalbital 50 mg, n = 392 (304 for efficacy) Placebo, n = 405 (320 for efficacy)
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 functional disability at 2 h Use of rescue medication Mean time to first use of rescue medication AEs Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated block randomization schedule"
Allocation concealment (selection bias)	Unclear risk	Not described, but probably remote allocation
Blinding (performance bias and detection bias) All outcomes	Low risk	"3 identical tablets for each dose". DD method
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs described. All treated attacks accounted for
Study size	Low risk	> 200 participants per treatment arm

ACE: angiotensin-converting enzyme; AE: adverse event; ARB: angiotensin receptor blocker; DB: double-blind; DD: double dummy; h: hour; IHS: International Headache Society; ITT: intention to treat; MAOI: monoamine oxidase inhibitor; N: number of participants in study; n: number of participants in treatment arm; NSAID: non-steroidal anti-inflammatory drug; PC: placebo-controlled; R: randomised; SJW: St John's Wort; W: withdrawals.

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

Study	Reason for exclusion
Cady 2014	No single dose data (treatment over 3 months)
Edwards 2013	Study of cognitive function over 2 h. Did not assess pain, associated symptoms, or adverse events
Krymchantowski 2000	Enriched enrolment study investigating recurrence
Landy 2009	Post hoc analysis of Landy 2007 (secondary publication under Brandes 2007 Study 1; Brandes 2007 Study 2)
Smith 2007	Long-term, open-label study. Data pertains to quality of life and satisfaction outcomes only and not outcomes specified in this review
TRX107563	Probable migraine. Participants with migraine according to IHS criteria were excluded
White 2011	Long-term study investigating effects of treatment on blood pressure. No single episode data for efficacy or adverse events
Winner 2007	Open-label safety study

IHS: International Headache Society.

DATA AND ANALYSES

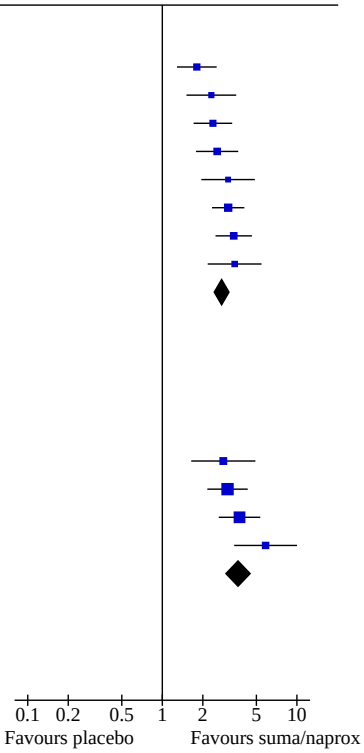
Comparison 1. Sumatriptan plus naproxen versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Pain-free at 2 h	12		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1.1 Mild baseline pain	8	3395	Risk Ratio (M-H, Fixed, 95% CI)	2.76 [2.43, 3.13]
1.1.2 Moderate/severe baseline pain	4	2596	Risk Ratio (M-H, Fixed, 95% CI)	3.65 [2.97, 4.49]
1.2 Headache relief at 2 h	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.2.1 Moderate/severe baseline pain	4	2596	Risk Ratio (M-H, Fixed, 95% CI)	2.16 [1.95, 2.39]
1.3 24-h sustained pain-free	12		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.3.1 Mild baseline pain	8	3396	Risk Ratio (M-H, Fixed, 95% CI)	3.04 [2.59, 3.56]
1.3.2 Moderate/severe baseline pain	4	2596	Risk Ratio (M-H, Fixed, 95% CI)	3.43 [2.69, 4.36]
1.4 24-h sustained headache relief	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.4.1 Moderate/severe baseline pain	4	2596	Risk Ratio (M-H, Fixed, 95% CI)	2.61 [2.27, 2.99]
1.5 Any adverse event	10	5616	Risk Ratio (M-H, Fixed, 95% CI)	1.76 [1.53, 2.03]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.5.1 Mild baseline pain	6	2823	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [1.16, 1.86]
1.5.2 Moderate/severe baseline pain	4	2793	Risk Ratio (M-H, Fixed, 95% CI)	1.97 [1.64, 2.37]
1.6 Rescue medication	12	5565	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.41, 0.48]
1.6.1 Mild baseline pain	8	3396	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.38, 0.47]
1.6.2 Moderate/severe baseline pain	4	2169	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.42, 0.53]
1.7 Relief of associated symptoms at 2 h	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.7.1 Nausea	8	1705	Risk Ratio (M-H, Fixed, 95% CI)	3.47 [2.79, 4.32]
1.7.2 Photophobia	8	3127	Risk Ratio (M-H, Fixed, 95% CI)	2.77 [2.44, 3.13]
1.7.3 Phonophobia	8	2856	Risk Ratio (M-H, Fixed, 95% CI)	2.63 [2.33, 2.97]
1.8 Relief of functional disability at 2 h	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.8.1 Mild baseline pain	2	981	Risk Ratio (M-H, Fixed, 95% CI)	2.91 [2.29, 3.72]
1.8.2 Moderate/severe baseline pain	3	1984	Risk Ratio (M-H, Fixed, 95% CI)	3.36 [2.63, 4.29]

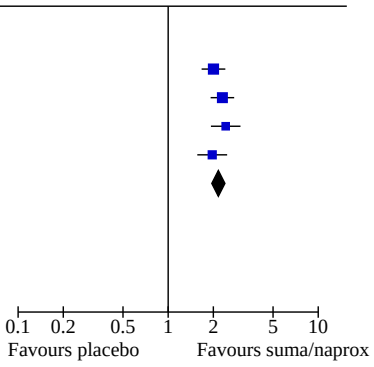
Analysis 1.1. Comparison 1: Sumatriptan plus naproxen versus placebo, Outcome 1: Pain-free at 2 h

Study or Subgroup	Suma/naprox Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Mild baseline pain						
Mannix 2009 Study 1	63	151	37	160	13.5%	1.80 [1.28 , 2.53]
Mathew 2009 Study 1	54	136	23	134	8.7%	2.31 [1.51 , 3.54]
Mannix 2009 Study 2	79	151	35	159	12.8%	2.38 [1.71 , 3.31]
Lipton 2009 Study 1	230	443	25	123	14.7%	2.55 [1.78 , 3.67]
Mathew 2009 Study 2	59	134	19	133	7.2%	3.08 [1.95 , 4.87]
Silberstein 2008 Study 1	146	280	50	296	18.3%	3.09 [2.34 , 4.07]
Silberstein 2008 Study 2	141	276	39	259	15.1%	3.39 [2.48 , 4.63]
Lipton 2009 Study 2	236	454	16	106	9.7%	3.44 [2.17 , 5.46]
Subtotal (95% CI)		**2025**		**1370**	**100.0%**	**2.76 [2.43 , 3.13]**
Total events:	1008		244			
Heterogeneity: Chi² = 11.07, df = 7 (P = 0.14); I² = 37%						
Test for overall effect: Z = 15.73 (P < 0.00001)						
1.1.2 Moderate/severe baseline pain						
TRX109011/13	45	317	16	320	16.0%	2.84 [1.64 , 4.92]
Brandes 2007 Study 2	107	362	37	382	36.2%	3.05 [2.16 , 4.31]
Brandes 2007 Study 1	125	364	33	360	33.4%	3.75 [2.63 , 5.34]
Smith 2005	85	250	14	241	14.3%	5.85 [3.42 , 10.01]
Subtotal (95% CI)		**1293**		**1303**	**100.0%**	**3.65 [2.97 , 4.49]**
Total events:	362		100			
Heterogeneity: Chi² = 4.83, df = 3 (P = 0.18); I² = 38%						
Test for overall effect: Z = 12.24 (P < 0.00001)						
Test for subgroup differences: Chi² = 5.13, df = 1 (P = 0.02), I² = 80.5%						



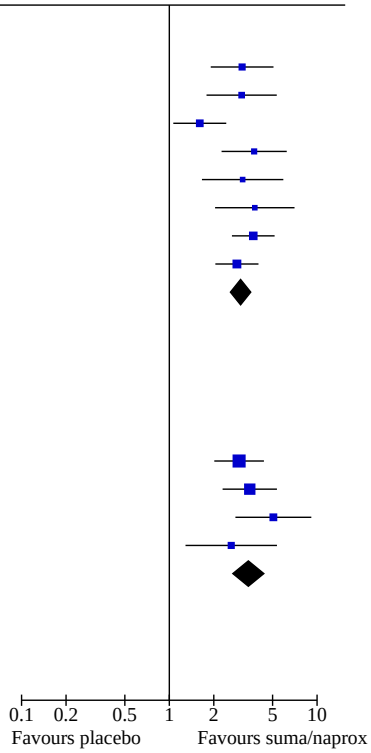
Analysis 1.2. Comparison 1: Sumatriptan plus naproxen versus placebo, Outcome 2: Headache relief at 2 h

Study or Subgroup	Suma/naprox Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Moderate/severe baseline pain						
Brandes 2007 Study 1	207	362	109	382	30.3%	2.00 [1.67 , 2.40]
Brandes 2007 Study 2	237	364	102	360	29.3%	2.30 [1.92 , 2.75]
Smith 2005	163	250	65	241	18.9%	2.42 [1.93 , 3.03]
TRX109011/13	148	317	76	320	21.6%	1.97 [1.56 , 2.47]
Subtotal (95% CI)		**1293**		**1303**	**100.0%**	**2.16 [1.95 , 2.39]**
Total events:	755		352			
Heterogeneity: Chi² = 2.70, df = 3 (P = 0.44); I² = 0%						
Test for overall effect: Z = 15.05 (P < 0.00001)						
Test for subgroup differences: Not applicable						



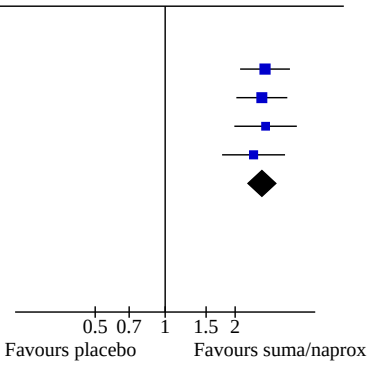
Analysis 1.3. Comparison 1: Sumatriptan plus naproxen versus placebo, Outcome 3: 24-h sustained pain-free

Study or Subgroup	Suma/naprox Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 Mild baseline pain						
Lipton 2009 Study 1	168	443	15	123	13.0%	3.11 [1.91 , 5.07]
Lipton 2009 Study 2	159	455	12	106	10.8%	3.09 [1.79 , 5.34]
Mannix 2009 Study 1	44	151	29	160	15.6%	1.61 [1.06 , 2.43]
Mannix 2009 Study 2	57	151	16	159	8.6%	3.75 [2.26 , 6.23]
Mathew 2009 Study 1	35	136	11	134	6.1%	3.14 [1.66 , 5.91]
Mathew 2009 Study 2	42	134	11	133	6.1%	3.79 [2.04 , 7.04]
Silberstein 2008 Study 1	126	280	36	296	19.3%	3.70 [2.65 , 5.16]
Silberstein 2008 Study 2	110	276	36	259	20.5%	2.87 [2.05 , 4.01]
Subtotal (95% CI)		**2026**		**1370**	**100.0%**	**3.04 [2.59 , 3.56]**
Total events:	741		166			
Heterogeneity: Chi² = 11.77, df = 7 (P = 0.11); I² = 41%						
Test for overall effect: Z = 13.75 (P < 0.00001)						
1.3.2 Moderate/severe baseline pain						
Brandes 2007 Study 1	90	364	30	360	39.3%	2.97 [2.02 , 4.37]
Brandes 2007 Study 2	83	362	25	382	31.7%	3.50 [2.29 , 5.35]
Smith 2005	63	250	12	241	15.9%	5.06 [2.80 , 9.14]
TRX109011/13	26	317	10	320	13.0%	2.62 [1.29 , 5.35]
Subtotal (95% CI)		**1293**		**1303**	**100.0%**	**3.43 [2.69 , 4.36]**
Total events:	262		77			
Heterogeneity: Chi² = 2.75, df = 3 (P = 0.43); I² = 0%						
Test for overall effect: Z = 10.01 (P < 0.00001)						



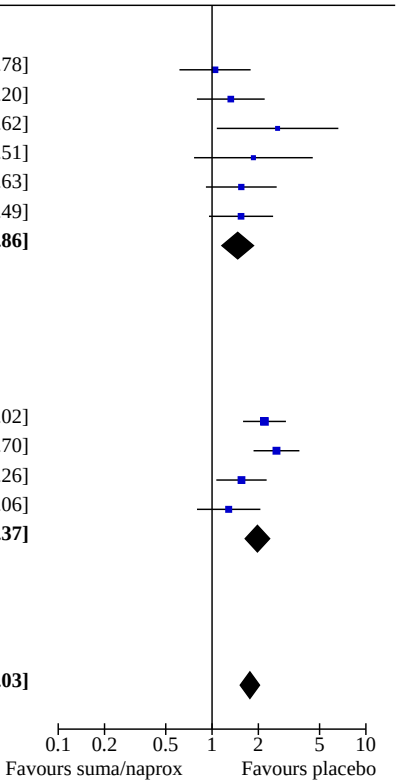
Analysis 1.4. Comparison 1: Sumatriptan plus naproxen versus placebo, Outcome 4: 24-h sustained headache relief

Study or Subgroup	Suma/naprox Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 Moderate/severe baseline pain						
Brandes 2007 Study 1	174	364	64	360	30.2%	2.69 [2.10 , 3.44]
Brandes 2007 Study 2	158	362	64	382	29.2%	2.61 [2.02 , 3.35]
Smith 2005	115	250	41	241	19.6%	2.70 [1.98 , 3.68]
TRX109011/13	107	317	45	320	21.0%	2.40 [1.76 , 3.28]
Subtotal (95% CI)		**1293**		**1303**	**100.0%**	**2.61 [2.27 , 2.99]**
Total events:	554		214			
Heterogeneity: Chi² = 0.38, df = 3 (P = 0.94); I² = 0%						
Test for overall effect: Z = 13.65 (P < 0.00001)						
Test for subgroup differences: Not applicable						



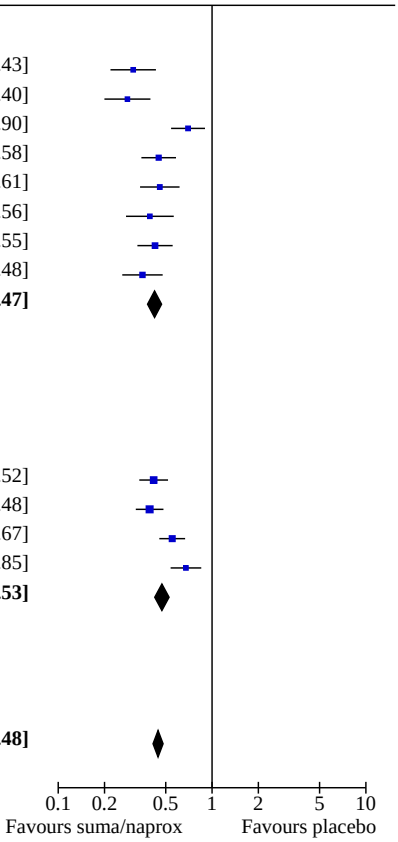
Analysis 1.5. Comparison 1: Sumatriptan plus naproxen versus placebo, Outcome 5: Any adverse event

Study or Subgroup	Suma/naprox Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.5.1 Mild baseline pain						
Lipton 2009 Study 1	57	447	15	123	9.3%	1.05 [0.61 , 1.78]
Lipton 2009 Study 2	85	458	15	107	9.6%	1.32 [0.80 , 2.20]
Mathew 2009 Study 1	16	144	6	144	2.4%	2.67 [1.07 , 6.62]
Mathew 2009 Study 2	13	139	7	139	2.8%	1.86 [0.76 , 4.51]
Silberstein 2008 Study 1	31	283	21	297	8.1%	1.55 [0.91 , 2.63]
Silberstein 2008 Study 2	39	278	24	264	9.7%	1.54 [0.96 , 2.49]
Subtotal (95% CI)		**1749**		**1074**	**41.7%**	**1.47 [1.16 , 1.86]**
Total events:	241		88			
Heterogeneity: Chi² = 3.72, df = 5 (P = 0.59); I² = 0%						
Test for overall effect: Z = 3.19 (P = 0.001)						
1.5.2 Moderate/severe baseline pain						
Brandes 2007 Study 1	100	370	45	365	17.8%	2.19 [1.59 , 3.02]
Brandes 2007 Study 2	97	367	39	387	15.0%	2.62 [1.86 , 3.70]
Smith 2005	58	251	36	242	14.4%	1.55 [1.07 , 2.26]
TRX109011/13	36	406	28	405	11.0%	1.28 [0.80 , 2.06]
Subtotal (95% CI)		**1394**		**1399**	**58.3%**	**1.97 [1.64 , 2.37]**
Total events:	291		148			
Heterogeneity: Chi² = 7.78, df = 3 (P = 0.05); I² = 61%						
Test for overall effect: Z = 7.31 (P < 0.00001)						
Total (95% CI)		**3143**		**2473**	**100.0%**	**1.76 [1.53 , 2.03]**
Total events:	532		236			
Heterogeneity: Chi² = 15.34, df = 9 (P = 0.08); I² = 41%						
Test for overall effect: Z = 7.72 (P < 0.00001)						
Test for subgroup differences: Chi² = 3.78, df = 1 (P = 0.05), I² = 73.5%						



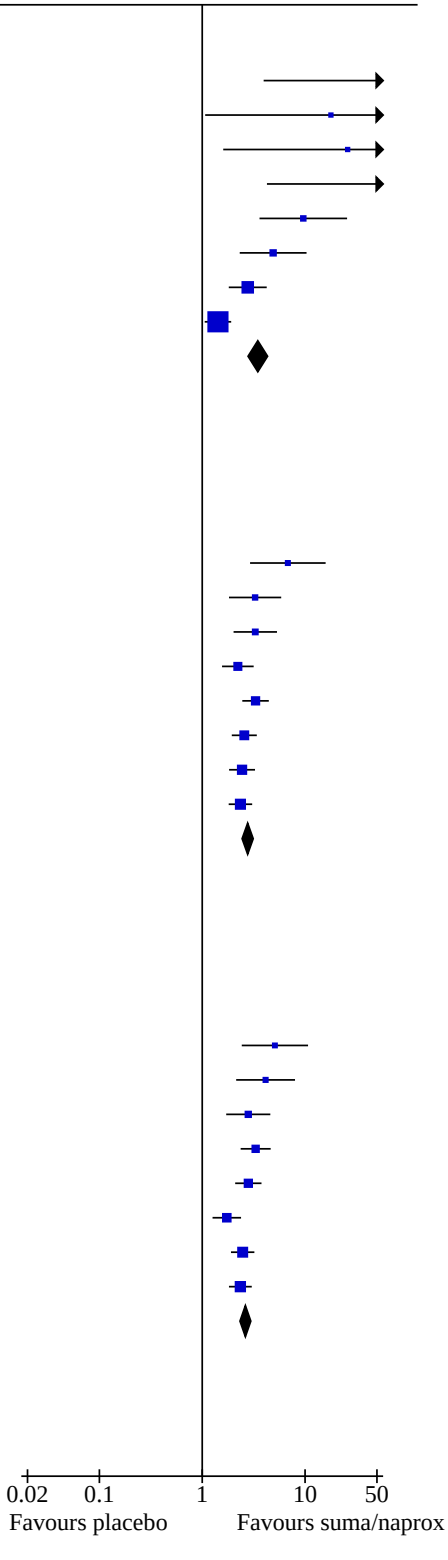
Analysis 1.6. Comparison 1: Sumatriptan plus naproxen versus placebo, Outcome 6: Rescue medication

Study or Subgroup	Suma/naprox Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.6.1 Mild baseline pain						
Lipton 2009 Study 1	52	443	47	123	5.3%	0.31 [0.22 , 0.43]
Lipton 2009 Study 2	52	455	43	106	5.0%	0.28 [0.20 , 0.40]
Mannix 2009 Study 1	56	151	85	160	5.9%	0.70 [0.54 , 0.90]
Mannix 2009 Study 2	47	151	110	159	7.7%	0.45 [0.35 , 0.58]
Mathew 2009 Study 1	39	136	84	134	6.1%	0.46 [0.34 , 0.61]
Mathew 2009 Study 2	29	134	73	133	5.3%	0.39 [0.28 , 0.56]
Silberstein 2008 Study 1	56	280	139	296	9.7%	0.43 [0.33 , 0.55]
Silberstein 2008 Study 2	44	276	117	259	8.7%	0.35 [0.26 , 0.48]
Subtotal (95% CI)		**2026**		**1370**	**53.8%**	**0.42 [0.38 , 0.47]**
Total events:	375		698			
Heterogeneity: Chi² = 25.76, df = 7 (P = 0.0006); I² = 73%						
Test for overall effect: Z = 16.14 (P < 0.00001)						
1.6.2 Moderate/severe baseline pain						
Brandes 2007 Study 1	81	364	192	360	13.9%	0.42 [0.34 , 0.52]
Brandes 2007 Study 2	83	362	223	382	15.6%	0.39 [0.32 , 0.48]
Smith 2005	88	250	154	241	11.3%	0.55 [0.45 , 0.67]
TRX109011/13	52	107	74	103	5.4%	0.68 [0.54 , 0.85]
Subtotal (95% CI)		**1083**		**1086**	**46.2%**	**0.47 [0.42 , 0.53]**
Total events:	304		643			
Heterogeneity: Chi² = 16.21, df = 3 (P = 0.001); I² = 81%						
Test for overall effect: Z = 13.79 (P < 0.00001)						
Total (95% CI)		**3109**		**2456**	**100.0%**	**0.45 [0.41 , 0.48]**
Total events:	679		1341			
Heterogeneity: Chi² = 45.47, df = 11 (P < 0.00001); I² = 76%						
Test for overall effect: Z = 21.22 (P < 0.00001)						
Test for subgroup differences: Chi² = 2.08, df = 1 (P = 0.15), I² = 51.8%						

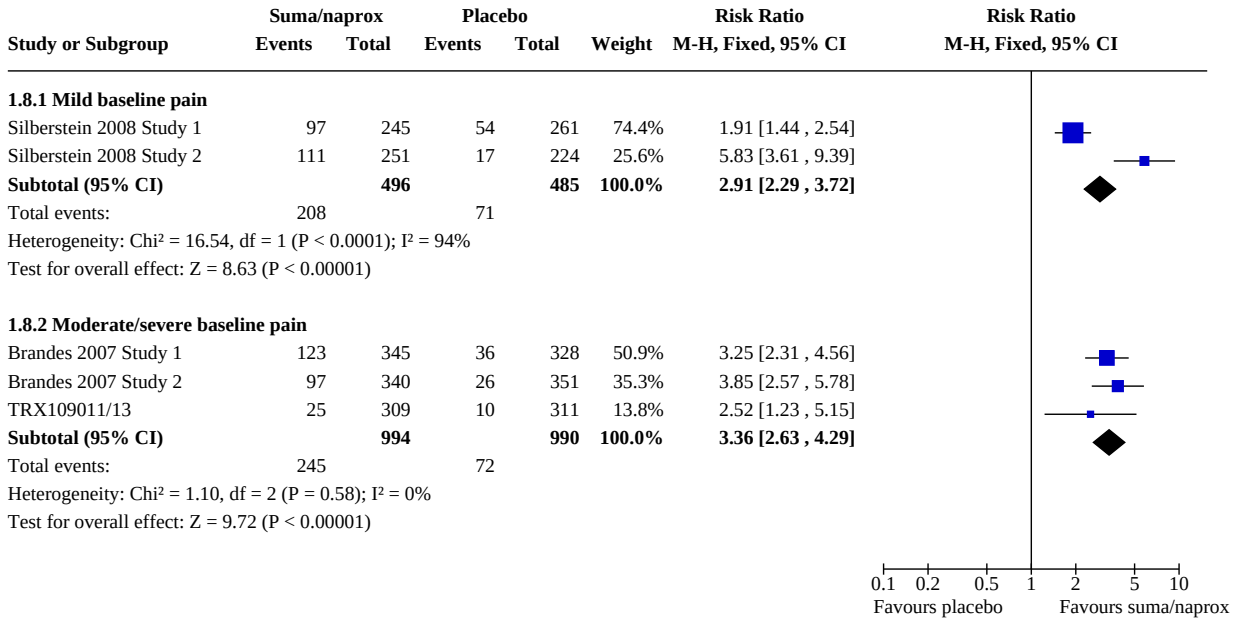


Analysis 1.7. Comparison 1: Sumatriptan plus naproxen versus placebo, Outcome 7: Relief of associated symptoms at 2 h

Study or Subgroup	Suma/naprox Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.7.1 Nausea						
Lipton 2009 Study 1	33	126	0	120	0.6%	63.83 [3.96 , 1030.28]
Mathew 2009 Study 1	9	48	0	45	0.6%	17.84 [1.07 , 297.81]
Mathew 2009 Study 2	15	48	0	40	0.6%	25.94 [1.60 , 420.39]
Lipton 2009 Study 2	41	124	0	102	0.6%	68.39 [4.26 , 1098.26]
Silberstein 2008 Study 2	44	95	4	83	4.8%	9.61 [3.61 , 25.61]
Silberstein 2008 Study 1	36	82	7	78	8.1%	4.89 [2.32 , 10.33]
Brandes 2007 Study 1	72	176	22	149	26.8%	2.77 [1.81 , 4.24]
Brandes 2007 Study 2	76	201	50	188	58.0%	1.42 [1.06 , 1.91]
Subtotal (95% CI)		**900**		**805**	**100.0%**	**3.47 [2.79 , 4.32]**
Total events:	326		83			
Heterogeneity: Chi² = 52.82, df = 7 (P < 0.00001); I² = 87%						
Test for overall effect: Z = 11.17 (P < 0.00001)						
1.7.2 Photophobia						
Lipton 2009 Study 2	170	305	5	61	3.1%	6.80 [2.92 , 15.84]
Mathew 2009 Study 1	38	95	12	98	4.5%	3.27 [1.82 , 5.86]
Mathew 2009 Study 2	53	101	16	100	6.1%	3.28 [2.02 , 5.33]
Lipton 2009 Study 1	185	309	24	89	14.1%	2.22 [1.56 , 3.16]
Silberstein 2008 Study 2	138	197	38	179	15.0%	3.30 [2.45 , 4.44]
Silberstein 2008 Study 1	112	197	47	212	17.1%	2.56 [1.94 , 3.39]
Brandes 2007 Study 2	118	300	50	310	18.6%	2.44 [1.82 , 3.26]
Brandes 2007 Study 1	135	288	57	286	21.6%	2.35 [1.81 , 3.06]
Subtotal (95% CI)		**1792**		**1335**	**100.0%**	**2.77 [2.44 , 3.13]**
Total events:	949		249			
Heterogeneity: Chi² = 10.43, df = 7 (P = 0.17); I² = 33%						
Test for overall effect: Z = 16.09 (P < 0.00001)						
1.7.3 Phonophobia						
Mathew 2009 Study 2	38	80	7	75	2.7%	5.09 [2.42 , 10.69]
Mathew 2009 Study 1	39	86	9	82	3.4%	4.13 [2.14 , 7.98]
Lipton 2009 Study 2	154	262	13	62	7.9%	2.80 [1.71 , 4.59]
Silberstein 2008 Study 1	97	168	33	189	11.6%	3.31 [2.36 , 4.63]
Silberstein 2008 Study 2	119	174	38	156	15.0%	2.81 [2.09 , 3.77]
Lipton 2009 Study 1	156	270	28	84	16.0%	1.73 [1.26 , 2.39]
Brandes 2007 Study 1	140	281	56	278	21.1%	2.47 [1.90 , 3.21]
Brandes 2007 Study 2	135	293	62	316	22.3%	2.35 [1.82 , 3.03]
Subtotal (95% CI)		**1614**		**1242**	**100.0%**	**2.63 [2.33 , 2.97]**
Total events:	878		246			
Heterogeneity: Chi² = 14.40, df = 7 (P = 0.04); I² = 51%						
Test for overall effect: Z = 15.63 (P < 0.00001)						



Analysis 1.8. Comparison 1: Sumatriptan plus naproxen versus placebo, Outcome 8: Relief of functional disability at 2 h



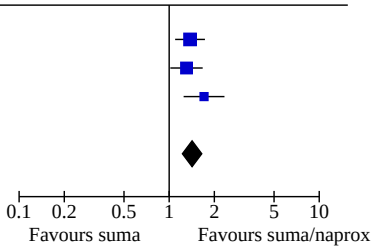
Comparison 2. Sumatriptan plus naproxen versus sumatriptan alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Pain-free at 2 h	3	1925	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [1.23, 1.65]
2.2 Headache relief at 2 h	3	1925	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [1.11, 1.29]
2.3 24-h sustained pain-free	3	1925	Risk Ratio (M-H, Fixed, 95% CI)	1.70 [1.41, 2.06]
2.4 24-h sustained headache relief	3	1925	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [1.24, 1.55]
2.5 Any adverse event	3	1952	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.86, 1.16]
2.6 Rescue medication	3	1925	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.58, 0.76]
2.7 Relief of associated symptoms at 2 h	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.7.1 Nausea	2	718	Risk Ratio (M-H, Fixed, 95% CI)	1.51 [1.21, 1.87]
2.7.2 Photophobia	2	1186	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [1.04, 1.39]
2.7.3 Phonophobia	2	1146	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [1.10, 1.45]
2.8 Relief of functional disability at 2 h	2	1354	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [1.18, 1.69]

Analysis 2.1. Comparison 2: Sumatriptan plus naproxen versus sumatriptan alone, Outcome 1: Pain-free at 2 h

Study or Subgroup	Suma/naprox Events	Total	Suma Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Brandes 2007 Study 1	125	364	90	361	41.1%	1.38 [1.10 , 1.73]
Brandes 2007 Study 2	107	362	82	362	37.3%	1.30 [1.02 , 1.67]
Smith 2005	85	250	45	226	21.5%	1.71 [1.25 , 2.34]
Total (95% CI)		**976**		**949**	**100.0%**	**1.42 [1.23 , 1.65]**
Total events:	317		217			

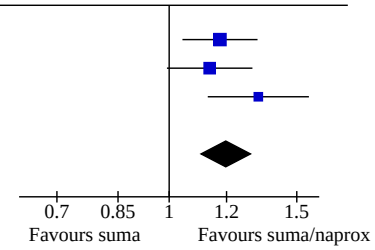
Heterogeneity: Chi² = 1.85, df = 2 (P = 0.40); I² = 0%
Test for overall effect: Z = 4.66 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2: Sumatriptan plus naproxen versus sumatriptan alone, Outcome 2: Headache relief at 2 h

Study or Subgroup	Suma/naprox Events	Total	Suma Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Brandes 2007 Study 1	237	364	200	361	40.2%	1.18 [1.04 , 1.32]
Brandes 2007 Study 2	207	362	182	362	36.4%	1.14 [0.99 , 1.30]
Smith 2005	163	250	111	226	23.3%	1.33 [1.13 , 1.56]
Total (95% CI)		**976**		**949**	**100.0%**	**1.20 [1.11 , 1.29]**
Total events:	607		493			

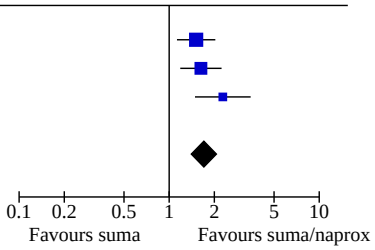
Heterogeneity: Chi² = 2.23, df = 2 (P = 0.33); I² = 10%
Test for overall effect: Z = 4.50 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2: Sumatriptan plus naproxen versus sumatriptan alone, Outcome 3: 24-h sustained pain-free

Study or Subgroup	Suma/naprox Events	Total	Suma Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Brandes 2007 Study 1	90	364	59	361	43.4%	1.51 [1.13 , 2.03]
Brandes 2007 Study 2	83	362	51	362	37.4%	1.63 [1.19 , 2.23]
Smith 2005	63	250	25	226	19.2%	2.28 [1.49 , 3.49]
Total (95% CI)		**976**		**949**	**100.0%**	**1.70 [1.41 , 2.06]**
Total events:	236		135			

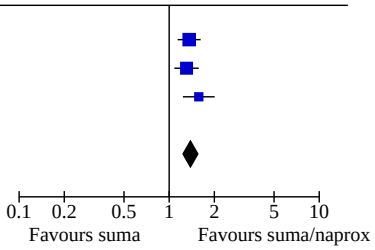
Heterogeneity: Chi² = 2.48, df = 2 (P = 0.29); I² = 19%
Test for overall effect: Z = 5.43 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2: Sumatriptan plus naproxen versus sumatriptan alone, Outcome 4: 24-h sustained headache relief

Study or Subgroup	Suma/naprox Events	Suma/naprox Total	Suma Events	Suma Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Brandes 2007 Study 1	174	364	127	361	40.1%	1.36 [1.14 , 1.62]
Brandes 2007 Study 2	158	362	121	362	38.1%	1.31 [1.08 , 1.57]
Smith 2005	115	250	66	226	21.8%	1.58 [1.23 , 2.01]
Total (95% CI)		**976**		**949**	**100.0%**	**1.39 [1.24 , 1.55]**
Total events:	447		314			

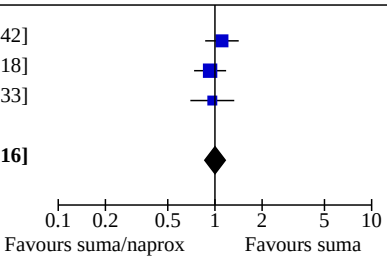
Heterogeneity: Chi² = 1.50, df = 2 (P = 0.47); I² = 0%
Test for overall effect: Z = 5.64 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 2.5. Comparison 2: Sumatriptan plus naproxen versus sumatriptan alone, Outcome 5: Any adverse event

Study or Subgroup	Suma/naprox Events	Suma/naprox Total	Suma Events	Suma Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Brandes 2007 Study 1	100	370	89	365	35.6%	1.11 [0.87 , 1.42]
Brandes 2007 Study 2	97	367	105	370	41.5%	0.93 [0.74 , 1.18]
Smith 2005	58	251	55	229	22.9%	0.96 [0.70 , 1.33]
Total (95% CI)		**988**		**964**	**100.0%**	**1.00 [0.86 , 1.16]**
Total events:	255		249			

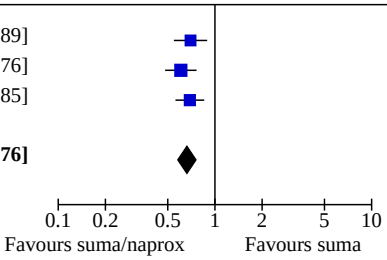
Heterogeneity: Chi² = 1.08, df = 2 (P = 0.58); I² = 0%
Test for overall effect: Z = 0.02 (P = 0.99)
Test for subgroup differences: Not applicable



Analysis 2.6. Comparison 2: Sumatriptan plus naproxen versus sumatriptan alone, Outcome 6: Rescue medication

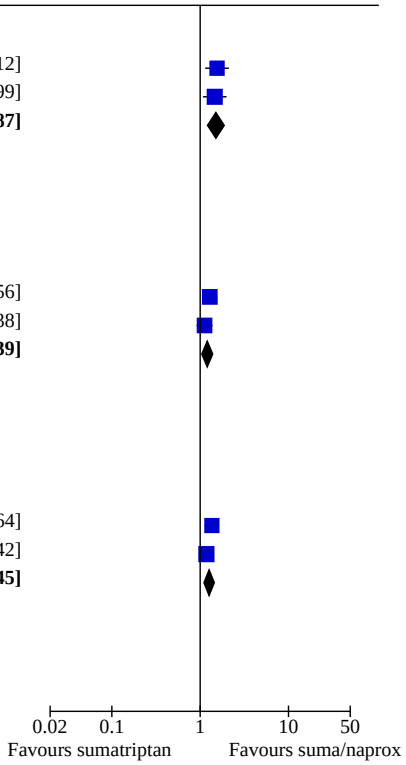
Study or Subgroup	Suma/naprox Events	Suma/naprox Total	Suma Events	Suma Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Brandes 2007 Study 1	81	364	115	361	30.9%	0.70 [0.55 , 0.89]
Brandes 2007 Study 2	83	362	137	362	36.7%	0.61 [0.48 , 0.76]
Smith 2005	88	250	115	226	32.4%	0.69 [0.56 , 0.85]
Total (95% CI)		**976**		**949**	**100.0%**	**0.66 [0.58 , 0.76]**
Total events:	252		367			

Heterogeneity: Chi² = 0.92, df = 2 (P = 0.63); I² = 0%
Test for overall effect: Z = 6.11 (P < 0.00001)
Test for subgroup differences: Not applicable



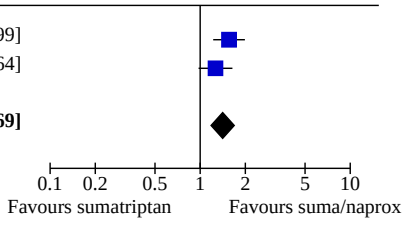
Analysis 2.7. Comparison 2: Sumatriptan plus naproxen versus sumatriptan alone, Outcome 7: Relief of associated symptoms at 2 h

Study or Subgroup	Suma/naprox Events	Suma/naprox Total	Suma Events	Suma Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.7.1 Nausea						
Brandes 2007 Study 1	72	176	44	167	48.3%	1.55 [1.14 , 2.12]
Brandes 2007 Study 2	76	201	45	174	51.7%	1.46 [1.07 , 1.99]
Subtotal (95% CI)		**377**		**341**	**100.0%**	**1.51 [1.21 , 1.87]**
Total events:	148		89			
Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I² = 0%						
Test for overall effect: Z = 3.68 (P = 0.0002)						
2.7.2 Photophobia						
Brandes 2007 Study 1	135	288	108	296	50.2%	1.28 [1.06 , 1.56]
Brandes 2007 Study 2	118	300	106	302	49.8%	1.12 [0.91 , 1.38]
Subtotal (95% CI)		**588**		**598**	**100.0%**	**1.20 [1.04 , 1.39]**
Total events:	253		214			
Heterogeneity: Chi² = 0.89, df = 1 (P = 0.35); I² = 0%						
Test for overall effect: Z = 2.55 (P = 0.01)						
2.7.3 Phonophobia						
Brandes 2007 Study 1	140	281	105	286	47.9%	1.36 [1.12 , 1.64]
Brandes 2007 Study 2	135	293	112	286	52.1%	1.18 [0.97 , 1.42]
Subtotal (95% CI)		**574**		**572**	**100.0%**	**1.26 [1.10 , 1.45]**
Total events:	275		217			
Heterogeneity: Chi² = 1.07, df = 1 (P = 0.30); I² = 7%						
Test for overall effect: Z = 3.39 (P = 0.0007)						



Analysis 2.8. Comparison 2: Sumatriptan plus naproxen versus sumatriptan alone, Outcome 8: Relief of functional disability at 2 h

Study or Subgroup	Suma/naprox Events	Suma/naprox Total	Suma Events	Suma Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Brandes 2007 Study 1	123	345	76	332	50.4%	1.56 [1.22 , 1.99]
Brandes 2007 Study 2	97	340	76	337	49.6%	1.27 [0.98 , 1.64]
Total (95% CI)		**685**		**669**	**100.0%**	**1.41 [1.18 , 1.69]**
Total events:	220		152			
Heterogeneity: Chi² = 1.31, df = 1 (P = 0.25); I² = 24%						
Test for overall effect: Z = 3.82 (P = 0.0001)						
Test for subgroup differences: Not applicable						



Comparison 3. Sumatriptan plus naproxen versus naproxen alone

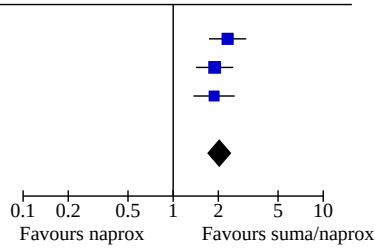
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Pain-free at 2 h	3	1944	Risk Ratio (M-H, Fixed, 95% CI)	2.03 [1.71, 2.40]
3.2 Headache relief at 2 h	3	1944	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [1.30, 1.54]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.3 24-h sustained pain-free	3	1944	Risk Ratio (M-H, Fixed, 95% CI)	2.25 [1.82, 2.78]
3.4 24-h sustained headache relief	3	1944	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [1.45, 1.85]
3.5 Any adverse event	3	1970	Risk Ratio (M-H, Fixed, 95% CI)	1.77 [1.47, 2.13]
3.6 Rescue medication	3	1944	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.54, 0.70]
3.7 Relief of associated symptoms at 2 h	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.7.1 Nausea	2	726	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.90, 1.32]
3.7.2 Photophobia	2	1176	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [1.19, 1.62]
3.7.3 Phonophobia	2	1135	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [1.28, 1.72]
3.8 Relief of functional disability at 2 h	2	1352	Risk Ratio (M-H, Fixed, 95% CI)	1.63 [1.35, 1.97]

Analysis 3.1. Comparison 3: Sumatriptan plus naproxen versus naproxen alone, Outcome 1: Pain-free at 2 h

Study or Subgroup	Suma/naprox Events	Suma/naprox Total	Naprox Events	Naprox Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Brandes 2007 Study 1	125	364	53	356	34.4%	2.31 [1.73 , 3.07]
Brandes 2007 Study 2	107	362	57	364	36.5%	1.89 [1.42 , 2.51]
Smith 2005	85	250	45	248	29.0%	1.87 [1.37 , 2.57]
Total (95% CI)		**976**		**968**	**100.0%**	**2.03 [1.71 , 2.40]**
Total events:	317		155			

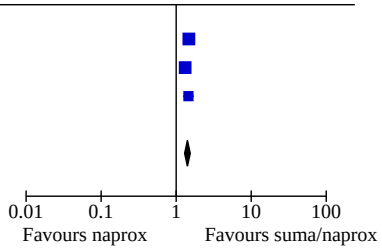
Heterogeneity: Chi² = 1.26, df = 2 (P = 0.53); I² = 0%
Test for overall effect: Z = 8.14 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 3.2. Comparison 3: Sumatriptan plus naproxen versus naproxen alone, Outcome 2: Headache relief at 2 h

Study or Subgroup	Suma/naprox Events	Suma/naprox Total	Naprox Events	Naprox Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Brandes 2007 Study 1	237	364	157	356	37.1%	1.48 [1.28 , 1.70]
Brandes 2007 Study 2	207	362	158	364	36.8%	1.32 [1.14 , 1.53]
Smith 2005	163	250	111	248	26.1%	1.46 [1.23 , 1.72]
Total (95% CI)		**976**		**968**	**100.0%**	**1.41 [1.30 , 1.54]**
Total events:	607		426			

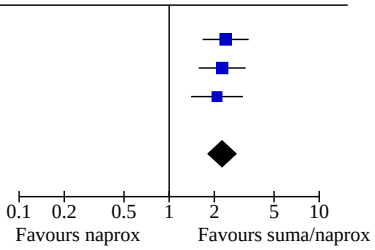
Heterogeneity: Chi² = 1.38, df = 2 (P = 0.50); I² = 0%
Test for overall effect: Z = 7.85 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 3.3. Comparison 3: Sumatriptan plus naproxen versus naproxen alone, Outcome 3: 24-h sustained pain-free

Study or Subgroup	Suma/naprox Events	Suma/naprox Total	Naprox Events	Naprox Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Brandes 2007 Study 1	90	364	37	356	35.8%	2.38 [1.67 , 3.39]
Brandes 2007 Study 2	83	362	37	364	35.3%	2.26 [1.58 , 3.23]
Smith 2005	63	250	30	248	28.8%	2.08 [1.40 , 3.10]
Total (95% CI)		**976**		**968**	**100.0%**	**2.25 [1.82 , 2.78]**
Total events:	236		104			

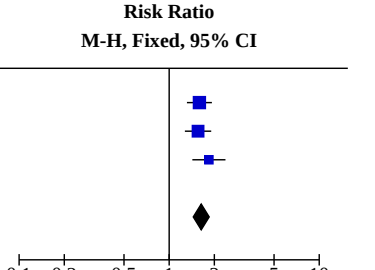
Heterogeneity: Chi² = 0.24, df = 2 (P = 0.89); I² = 0%
Test for overall effect: Z = 7.47 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 3.4. Comparison 3: Sumatriptan plus naproxen versus naproxen alone, Outcome 4: 24-h sustained headache relief

Study or Subgroup	Suma/naprox Events	Suma/naprox Total	Naprox Events	Naprox Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Brandes 2007 Study 1	174	364	107	356	39.8%	1.59 [1.31 , 1.93]
Brandes 2007 Study 2	158	362	102	364	37.4%	1.56 [1.27 , 1.91]
Smith 2005	115	250	62	248	22.9%	1.84 [1.43 , 2.37]
Total (95% CI)		**976**		**968**	**100.0%**	**1.64 [1.45 , 1.85]**
Total events:	447		271			

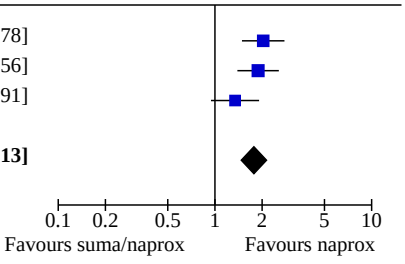
Heterogeneity: Chi² = 1.13, df = 2 (P = 0.57); I² = 0%
Test for overall effect: Z = 7.91 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 3.5. Comparison 3: Sumatriptan plus naproxen versus naproxen alone, Outcome 5: Any adverse event

Study or Subgroup	Suma/naprox Events	Suma/naprox Total	Naprox Events	Naprox Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Brandes 2007 Study 1	100	370	48	361	33.9%	2.03 [1.49 , 2.78]
Brandes 2007 Study 2	97	367	52	371	36.1%	1.89 [1.39 , 2.56]
Smith 2005	58	251	43	250	30.0%	1.34 [0.94 , 1.91]
Total (95% CI)		**988**		**982**	**100.0%**	**1.77 [1.47 , 2.13]**
Total events:	255		143			

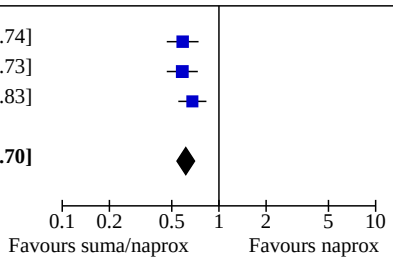
Heterogeneity: Chi² = 3.26, df = 2 (P = 0.20); I² = 39%
Test for overall effect: Z = 6.07 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 3.6. Comparison 3: Sumatriptan plus naproxen versus naproxen alone, Outcome 6: Rescue medication

Study or Subgroup	Suma/naprox Events	Total	Naprox Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Brandes 2007 Study 1	81	364	135	356	33.4%	0.59 [0.46 , 0.74]
Brandes 2007 Study 2	83	362	143	364	34.9%	0.58 [0.46 , 0.73]
Smith 2005	88	250	129	248	31.7%	0.68 [0.55 , 0.83]
Total (95% CI)		**976**		**968**	**100.0%**	**0.61 [0.54 , 0.70]**
Total events:	252		407			

Heterogeneity: Chi² = 1.19, df = 2 (P = 0.55); I² = 0%
Test for overall effect: Z = 7.43 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 3.7. Comparison 3: Sumatriptan plus naproxen versus naproxen alone, Outcome 7: Relief of associated symptoms at 2 h

Study or Subgroup	Suma/naprox Events	Total	Naprox Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.7.1 Nausea						
Brandes 2007 Study 1	72	176	66	174	50.9%	1.08 [0.83 , 1.40]
Brandes 2007 Study 2	76	201	60	175	49.1%	1.10 [0.84 , 1.45]
Subtotal (95% CI)		**377**		**349**	**100.0%**	**1.09 [0.90 , 1.32]**
Total events:	148		126			

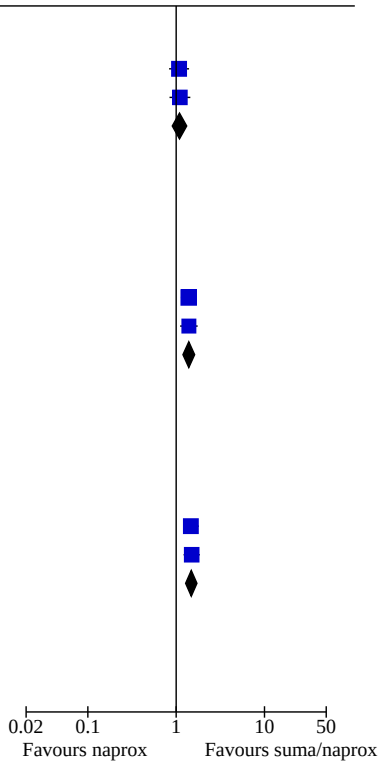
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.91); I² = 0%
Test for overall effect: Z = 0.90 (P = 0.37)

3.7.2 Photophobia						
Brandes 2007 Study 1	135	288	97	287	53.4%	1.39 [1.13 , 1.70]
Brandes 2007 Study 2	118	300	85	301	46.6%	1.39 [1.11 , 1.75]
Subtotal (95% CI)		**588**		**588**	**100.0%**	**1.39 [1.19 , 1.62]**
Total events:	253		182			

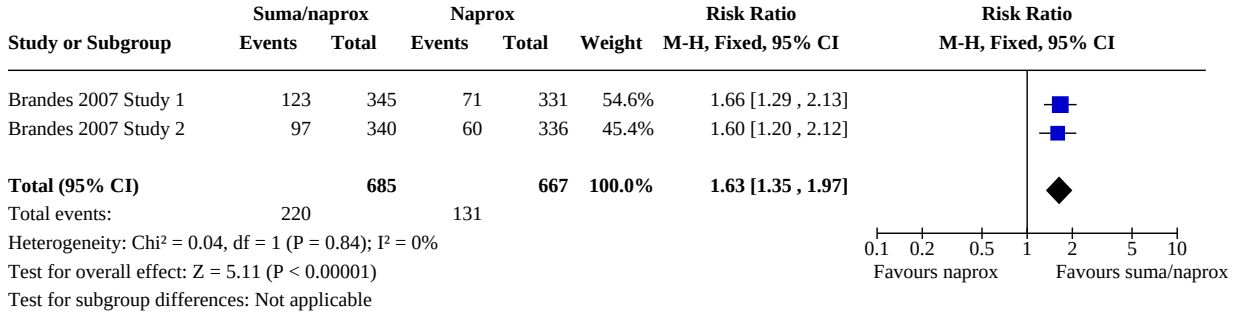
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.98); I² = 0%
Test for overall effect: Z = 4.24 (P < 0.0001)

3.7.3 Phonophobia						
Brandes 2007 Study 1	140	281	90	265	50.6%	1.47 [1.20 , 1.80]
Brandes 2007 Study 2	135	293	91	296	49.4%	1.50 [1.21 , 1.85]
Subtotal (95% CI)		**574**		**561**	**100.0%**	**1.48 [1.28 , 1.72]**
Total events:	275		181			

Heterogeneity: Chi² = 0.02, df = 1 (P = 0.89); I² = 0%
Test for overall effect: Z = 5.25 (P < 0.00001)



Analysis 3.8. Comparison 3: Sumatriptan plus naproxen versus naproxen alone, Outcome 8: Relief of functional disability at 2 h



APPENDICES

Appendix 1. Definitions

All terms relating to primary efficacy outcomes are defined according to the effect of the treatment on headache pain, measured using a 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.
- 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.
- 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.
- Relief of functional disability - reduction in the level of functional disability, measured using a 4-point scale, from moderate or severe disability (grade 2/3) at baseline to mild or none (grade 1/0) at two hours after administration of study medication, expressed as a fraction of the treated participants with moderate or severe functional disability at baseline.

Appendix 2. Search strategy for CENTRAL (via CRSO)

1. MESH DESCRIPTOR sumatriptan EXPLODE ALL TREES (318)
2. MESH DESCRIPTOR naproxen EXPLODE ALL TREES (804)
3. 1 AND 2 (21)
4. (sumatriptan AND naproxen) OR Treximet OR Trexima:TI,AB,KY (43)
5. 3 OR 4 (34)
6. MeSH descriptor Migraine Disorders explode all trees (1513)
7. (headach* OR migrain* OR cephalgi* OR cephalalgi*):TI,AB,KY (17752)
8. 6 OR 7 (17752)
9. 5 AND 8 (43)

Appendix 3. Search strategy for MEDLINE (via Ovid)

1. Sumatriptan/ AND Naproxen/ (62)

2. (sumatriptan AND naproxen) OR Treximet OR Trexima.mp (87)
3. 1 OR 2 (87)
4. exp Migraine Disorders/ (23046)
5. (headach* OR migrain* OR cephalgi* OR cephalalgi*).mp. (83223)
6. 4 OR 5 (83229)
7. randomized controlled trial.pt. (411120)
8. controlled clinical trial.pt. (91645)
9. randomized.ab. (303323)
10. placebo.ab. (157443)
11. drug therapy.fs. (1836743)
12. randomly.ab. (214805)
13. trial.ab. (315410)
14. groups.ab. (1354686)
15. 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 (3463859)
16. 3 AND 6 AND 15 (75)

Appendix 4. Search strategy for EMBASE (via Ovid)

1. Naproxen plus Sumatriptan/ (119)
2. (sumatriptan AND naproxen) OR Treximet OR Trexima.mp (1015)
3. 1 OR 2 (1015)
4. exp Migraine/ (47593)
5. (headach* OR migrain* OR cephalgi* OR cephalalgi*).mp. (229757)
6. 4 OR 5 (229757)
7. clinical trial.sh. (855551)
8. controlled clinical trial.sh. (392867)
9. randomized controlled trial.sh. (387381)
10. double-blind procedure.sh. (126282)
11. (clin* adj25 trial*).ab. (370068)
12. ((doubl* or trebl* or tripl*) adj25 (blind* or mask*)).ab. (151002)
13. placebo*.ab. (219229)
14. random*.ab. (1000145)
15. 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 (1868810)
16. 3 AND 6 AND 15 (328)

Appendix 5. GRADE: criteria for assigning grade of evidence

The GRADE system uses the following criteria for assigning grade of evidence (GRADEpro GDT 2015).

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

We decrease grade if we find:

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

We increase grade if we find:

- strong evidence of association - significant relative risk of > 2 (< 0.5) based on consistent evidence from two or more; observational studies, with no plausible confounders (+1);
- very strong evidence of association - significant relative risk of > 5 (< 0.2) based on direct evidence with no major threats to validity (+2);
- evidence of a dose response gradient (+1);
- that all plausible confounders would have reduced the effect (+1).

Appendix 6. Summary of outcomes: efficacy and use of rescue medication

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) suma/naprox 85/500 mg, n = 370 (2) suma 85 mg, n = 365 (3) naprox 500 mg, n = 361 (4) placebo, n = 365	No data	(1) 237/364 (2) 200/361 (3) 157/356 (4) 102/360	(1)125/364 (2) 90/361 (3) 53/356 (4) 33/360	(1) 174/364 (2) 127/361 (3) 107/365 (4) 64/360	(1) 90/364 (2) 59/361 (3) 37/356 (4) 30/360	From 2 to 24 h (1) 81/364 (2) 115/361 (3) 135/356 (4) 192/360
Brandes 2007 Study 2	(1) suma/naprox 85/500 mg, n = 367 (2) suma 85 mg, n = 370 (3) naprox 500 mg, n = 371 (4) placebo, n = 387	No data	(1) 207/362 (2) 182/362 (3) 158/364 (4) 109/382	(1)107/362 (2) 82/362 (3) 57/364 (4) 37/382	(1) 158/362 (2) 121/362 (3) 102/364 (4) 64/382	(1) 83/362 (2) 51/362 (3) 37/364 (4) 25/382	From 2 to 24 h (1) 83/362 (2) 137/362 (3) 143/364 (4) 223/382
Calhoun 2014	(1) suma/naprox 85/500 mg, n = 43 (2) placebo n = 43	No data	No data	(1) 63.9% (2) 33.3%	No data	(1) 69.1% (2) 23.3%	No data
Lipton 2009 Study 1	(1) suma/naprox 85/500 mg, n = 447 (1693 attacks) (2) placebo, n = 123 (424 attacks)	No data	No data	1st attack: (1) 230/443 (2) 25/123 All attacks: (1) 856/1665 (2) 106/422	No data	1st attack: (1) 168/443 (2) 15/123 All attacks: (1) 608/1665 (2) 72/422	From 2 to 24 h 1st attack: (1) 52/443 (2) 47/123 All attacks: (1) 197/1668 (2) 141/422
Lipton 2009 Study 2	(1) suma/naprox 85/500 mg, n = 458 (1678 attacks) (2) placebo, n = 107 (422 attacks)	No data	No data	1st attack: (1) 236/454 (2) 16/106 All attacks:	No data	1st attack: (1) 159/455 (2) 12/106 All attacks:	1st attack: (1) 52/455 (2) 43/106 All attacks:

(Continued)

				(1) 833/1655 (2) 83/416		(1) 564/1655 (2) 52/416	(1) 183/1662 (2) 144/416
Mannix 2009 Study 1	(1) suma/naprox 85/500 mg, n = 152 (2) placebo, n = 160	No data	No data	(1) 63/151 (2) 37/160	No data	(1) 44/151 (2) 29/160	From 2 to 48 h (1) 56/151 (2) 85/160
Mannix 2009 Study 2	(1) suma/naprox 85/500 mg, n = 151 (2) placebo, n = 160	No data	No data	(1) 79/151 (2) 35/159	No data	(1) 57/151 (2) 16/159	From 2 to 48 h (1) 47/151 (2) 110/159
Mathew 2009 Study 1	(1) suma/naprox 85/500 mg, n = 136 (2) placebo, n = 134	No data	No data	(1) 54/136 (2) 23/134	No data	(1) 35/136 (2) 11/134	From 2 to 24 h (1) 39/136 (2) 84/134
Mathew 2009 Study 2	(1) suma/naprox 85/500 mg, n = 134 (2) placebo, n =133	No data	No data	(1) 59/134 (2) 19/133	No data	(1) 42/134 (2) 11/133	From 2 to 24 h (1) 29/134 (2) 73/133
Silberstein 2008 Study 1	(1) suma/naprox 85/500 mg, n = 280 (2) placebo, n = 296	No data	No data	(1) 146/280 (2) 50/296	No data	(1) 126/280 (2) 36/296	From 2 to 24 h (1) 56/280 (2) 139/296
Silberstein 2008 Study 2	(1) suma/naprox 85/500 mg, n = 276 (2) placebo, n = 259	No data	No data	(1) 141/276 (2) 39/259	No data	(1) 110/276 (2) 36/259	From 2 to 24 h (1) 44/276 (2) 117/259
Smith 2005	(1) suma/naprox 50/500 mg, n = 250 (2) suma 50 mg, n = 229 (3) naprox 500 mg, n = 250 (4) placebo, n = 241	(1) 73/250 (2) 52/226 (3) 67/248 (4) 29/241	(1) 163/250 (2) 111/226 (3) 114/248 (4) 65/241	(1) 85/250 (2) 45/226 (3) 45/248 (4) 14/241	(1) 115/250 (2) 66/226 (3) 62/248 (4) 41/241	(1) 63/250 (2) 25/226 (3) 30/248 (4) 12/241	From 2 to 24 h (1) 88/250 (2) 115/226 (3) 129/248

(Continued)

							(4) 154/241
TRX109011/132	2010	(1) suma/naprox 85/500 mg, n = 317 (2) BCM, n = 304 (3) placebo, n = 320	No data	(1) 148/317 (2) 114/304 (3) 76/320	(1) 45/317 (2) 26/304 (3) 16/320	(1) 107/317 (2) 67/304 (3) 45/320	(1) 26/317 (2) 18/304 (3) 10/320	First dose only From 2 to 24 h (possibly 48 h) (1) 52/107 (2) 67/108 (3) 74/103

BCM: butalbital-containing combination medication (butalbital 50 mg, paracetamol (acetaminophen) 325 mg, and caffeine 40 mg); HR: headache relief; naprox: naproxen; PF: pain-free; SHR: sustained headache relief; SPF: sustained pain-free; suma: sumatriptan; suma/naprox: sumatriptan plus naproxen.

Appendix 7. Summary of outcomes: adverse events and withdrawals

Study ID	Treatment	Any AE	SAE	AE withdrawal	Other withdrawal
Brandes 2007 Study 1	(1) suma/naprox 85/500 mg, n = 370 (2) suma 85 mg, n = 365 (3) naprox 500 mg, n = 361 (4) placebo, n = 365	≤ 24 h: (1) 100/370 (2) 89/365 (3) 48/361 (4) 45/365	No SAE with combination, naproxen alone, or placebo in either study. 1 person admitted to hospital with palpitations following sumatriptan 85 mg	1 person in (2) with palpitations	Exclusions - took medication but no evaluable data: (1) 6 (2) 4 (3) 5 (4) 5
Brandes 2007 Study 2	(1) suma/naprox 85/500 mg, n = 367 (2) suma 85 mg, n = 370 (3) naprox 500 mg, n = 371 (4) placebo, n = 387	≤ 24 h: (1) 97/367 (2) 105/370 (3) 52/371 (4) 39/387	No SAE	None	Exclusions - took medication but no evaluable data: (1) 5 (2) 8 (3) 7 (4) 5
Calhoun 2014	(1) suma/naprox 85/500 mg, n = 43 (2) placebo n = 43	No data	No data	No data	No data
Lipton 2009 Study 1	(1) suma/naprox 85/500 mg, n = 447 (1693 attacks) (2) placebo, n = 123 (424 attacks)	≤ 72 h: Study 1, 1st attack: (1) 57/447 (2) 15/123 All attacks: (1) 153/1693 (2) 28/424	7 SAE across both studies, but judged not related to study medication, and occurred > 72 h after taking study medication. No details of groups	(1) 8 (3 chest discomfort) (2) 0 All judged related to study medication; mild/mod severity	People lost to follow-up or withdrawn for any attack: (1) < 6% (2) < 8%
Lipton 2009 Study 2	(1) suma/naprox 85/500 mg, n = 458 (1678 attacks) (2) placebo, n = 107 (422 attacks)	≤ 72 h: 1st attack: (1) 85/458 (2) 15/107 All attacks: (1) 219/1678		(1) 6 (3 chest discomfort, 3 nausea) (2) 1 (nausea) All judged	People lost to follow-up or withdrawn for any attack: (1) < 6% (2) < 7%

(Continued)

		(2) 36/422		related to study medication; mild/mod severity	
Mannix 2009 Study 1	(1) suma/naprox 85/500 mg, n = 152 (2) placebo, n = 160	≤ 48 h (possibly 24 h) AEs consistent with known profile of 2 drugs Drug-related AE frequency < 1%	None	None	Excluded from efficacy analysis: (1) 1 (2) 0
Mannix 2009 Study 2	(1) suma/naprox 85/500 mg, n = 151 (2) placebo, n = 160	≤ 48 h (possibly 24 h) AEs consistent with known profile of 2 drugs Drug-related AE frequency < 5%	None	None	Excluded from efficacy analysis: (1) 0 (2) 1
Mathew 2009 Study 1	(1) suma/naprox 85/500 mg, n = 144 (2) placebo, n = 144	Assume AE reported for safety population within 24 h (1) 16/144 (2) 6/144	None reported	1 AE withdrawal following placebo	5 people in (1) and (2) took medication, but not included in ITT. Unclear, but probably had no post-baseline efficacy data
Mathew 2009 Study 2	(1) suma/naprox 85/500 mg, n = 139 (2) placebo, n = 139	Assume AE reported for safety population within 24 h (1) 13/139 (2) 7/139	None reported	None	2 people in (1) and (2) took medication, but not included in ITT. Unclear, but probably had no post-baseline efficacy data
Silberstein 2008 Study 1	(1) suma/naprox 85/500 mg, n = 283 (2) placebo, n = 297	AE reported for safety population during study period (up to 1 week) (1) 31/283 (2) 21/297	None	None	3 people in (1) and 1 in (2) took medication but had no post-baseline efficacy data
Silberstein 2008 Study 2	(1) suma/naprox 85/500 mg, n = 278 (2) placebo, n = 264	AE reported for safety population during study period (up to 1 week) (1) 39/278 (2) 24/264	None	None	2 people in (1) and 5 in (2) took medication but had no post-baseline efficacy data
Smith 2005	(1) suma/naprox 50/500 mg, n = 251 (2) suma 50 mg, n = 229 (3) naprox 500 mg, n = 250 (4) placebo, n = 241	AE reported for safety population up to 72 h (1) 58/251 (2) 55/242 (3) 43/250 (4) 36/242	None	None	None reported

(Continued)

TRX109011/13 2010	(1) suma/naprox 85/500 mg, n = 317 (2) BCM, n = 392 (3) placebo, n = 320	AE for safety population reported within 72 h: (1) 36/406 (2) 21/392 (3) 28/405	(1) 2 (breast cancer diagnosis, chest pain, and hypertension) (2) 0 (3) 1 (intestinal mass and viral meningitis) None considered related to study medication	(1) 3, (2) 0, (3) 1	4 in total; pregnancy (2), breast cancer diagnosis (1), and use of prohibited medication (1)

AE: adverse event; BCM: barbiturate-containing medication; h: hour; naprox: naproxen; ITT: intention to treat; SAE: serious adverse event; suma: sumatriptan; suma/naprox: sumatriptan plus naproxen.

Appendix 8. 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 the reported use of rescue medication was measured was 24 hours (or possibly 48 hours in Mannix 2009 Study 1; Mannix 2009 Study 2; TRX109011/13). A survival curve published in Deroiser 2011 (TRX109011/13) shows that the vast majority of participants who take rescue medication do so within six hours of initial treatment, so we have combined data for 24 and 48 hours.

Significantly fewer participants used rescue medication with the combination than with placebo or either component alone (Analysis 1.6; Analysis 2.6; Analysis 3.6).

Summary of results: use of rescue medication

	Baseline pain	Studies	Attacks treated	Treatment (%)	Comparator (%)	Risk ratio (95% CI)	NNTp (95% CI)
Sumatriptan plus naproxen 85/500 mg vs placebo	mild	8	3396	19	51	0.42 (0.38 to 0.47)	3.1 (2.8 to 3.4)
Sumatriptan plus naproxen 85/500 mg vs placebo	≥ mod	4	2169	28	59	0.47 (0.42 to 0.53)	3.2 (2.9 to 3.7)
Sumatriptan plus naproxen 50-85/500 mg vs sumatriptan 50-85 mg	≥ mod	3	1925	26	39	0.66 (0.58 to 0.76)	7.8 (5.9 to 11)
Sumatriptan plus naproxen 50-85/500 mg vs naproxen 500 mg	≥ mod	3	1944	26	42	0.61 (0.54 to 0.70)	6.2 (4.9 to 8.3)

CI: confidence interval; NNTp: number needed to treat to prevent one event.

Relief of headache-associated symptoms

Eight studies provided data on relief of nausea, photophobia, and phonophobia in comparisons of sumatriptan plus naproxen versus placebo (Brandes 2007 Study 1; Brandes 2007 Study 2; Lipton 2009 Study 1; Lipton 2009 Study 2; Mathew 2009 Study 1; Mathew 2009 Study 2; Silberstein 2008 Study 1; Silberstein 2008 Study 2). Too few participants experienced vomiting to allow any analysis of this symptom. Two studies provided data comparing sumatriptan plus naproxen versus both sumatriptan and naproxen alone (Brandes 2007 Study 1; Brandes 2007 Study 2). Medication was taken when pain intensity was moderate or severe. Too few participants experienced vomiting to allow any analysis of this symptom.

For all symptoms, the combination was better than either placebo or the individual components, except for nausea relief with naproxen 500 mg alone, which was not statistically different from the combination. Lower (better) NNTs were obtained for all three symptoms in comparisons with placebo than for comparisons with individual components, and for photophobia and phonophobia relief in comparisons with naproxen alone than for sumatriptan alone (Analysis 1.7; Analysis 2.7; Analysis 3.7).

Summary of results: relief of associated symptoms at two hours

Intervention	Studies	Attacks with symptom present	Treatment (%)	Control (%)	Risk ratio (95% CI)	NNT (95% CI)
Nausea						
Sumatriptan plus naproxen 85/500 mg vs placebo	8	1705	36	10	3.5 (2.8 to 4.3)	3.9 (3.4 to 4.5)
Sumatriptan plus naproxen 85/500 mg vs sumatriptan 85 mg	2	718	39	26	1.5 (1.2 to 1.9)	7.6 (5.0 to 16)
Sumatriptan plus naproxen 85/500 mg vs naproxen 500 mg	2	726	39	36	1.1 (0.90 to 1.3)	not calculated
Photophobia						
Sumatriptan plus naproxen 85/500 mg vs placebo	8	3127	53	19	2.8 (2.4 to 3.1)	2.9 (2.7 to 3.2)
Sumatriptan plus naproxen 85/500 mg vs sumatriptan 85 mg	2	1186	43	36	1.2 (1.04 to 1.4)	14 (7.8 to 59)
Sumatriptan plus naproxen 85/500 mg vs naproxen 500 mg	2	1176	43	31	1.4 (1.2 to 1.6)	8.3 (5.7 to 15)
Phonophobia						
Sumatriptan plus naproxen 85/500 mg vs placebo	8	2856	54	20	2.6 (2.3 to 3.0)	2.9 (2.6 to 3.2)
Sumatriptan plus naproxen 85/500 mg vs sumatriptan 85 mg	2	1146	48	38	1.3 (1.1 to 1.5)	10 (6.4 to 23)
Sumatriptan plus naproxen 85/500 mg vs naproxen 500 mg	2	1135	48	32	1.5 (1.3 to 1.7)	6.4 (4.7 to 10)

CI: confidence interval; NNT: number needed to treat for an additional beneficial outcome.

Relief of functional disability

Two studies treating when pain was still mild (Silberstein 2008 Study 1; Silberstein 2008 Study 2), and three treating when pain was moderate or severe (Brandes 2007 Study 1; Brandes 2007 Study 2; TRX109011/13), reported on participants with functional disability at baseline and at two hours. Two of these studies provided data comparing sumatriptan/naproxen with both sumatriptan and naproxen alone (Brandes 2007 Study 1; Brandes 2007 Study 2). Medication was taken when pain intensity was moderate or severe.

The combination was effective at relieving functional disability when compared with placebo or either component alone (Analysis 1.8; Analysis 2.8; Analysis 3.8). Treating early, when pain was still mild, was significantly better than treating once pain was moderate or severe ($z = 3.132$, P value = 0.0016).

Summary of results: complete relief of functional disability at two hours

	Baseline pain	Studies	Attacks treated	Treatment (%)	Comparator (%)	Risk ratio (95% CI)	NNT (95% CI)
Sumatriptan plus naproxen 85/500 mg vs placebo	mild	2	981	42	14	2.9 (2.3 to 3.7)	3.7 (3.1 to 4.6))
Sumatriptan plus naproxen 85/500 mg vs placebo	≥ mod	3	1984	25	7.3	3.4 (2.6 to 4.3)	5.8 (4.9 to 7.0)
Sumatriptan plus naproxen 85/500 mg vs sumatriptan 85 mg	≥ mod	2	1354	32	23	1.4 (1.2 to 1.7)	11 (7.1 to 21)
Sumatriptan plus naproxen 85/500 mg vs naproxen 500 mg	≥ mod	2	1352	32	20	1.6 (1.4 to 2.0)	8.0 (5.9 to 13)

CI: confidence interval; mod: moderate; NNT: number needed to treat for an additional beneficial outcome.

WHAT'S NEW

Date	Event	Description
8 July 2020	Review declared as stable	See Published notes for up to date information about this stable review.

HISTORY

Protocol first published: Issue 6, 2010
Review first published: Issue 10, 2013

Date	Event	Description
29 May 2019	Amended	Contact details updated.
11 October 2017	Review declared as stable	No new studies likely to change the conclusions are expected.
20 April 2016	Review declared as stable	See Published notes.
28 October 2015	New search has been performed	New searches. One new study (43 participants) satisfied inclusion criteria (Calhoun 2014)
28 October 2015	New citation required but conclusions have not changed	The new study did not contribute data to any analyses. Minor changes were made to the Risk of bias assessment, in line with current standards.
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

SL and SD wrote the protocol.

For the earlier review, SL and SD carried out searches, study selection, data extraction, and analyses. RAM acted as arbitrator. All review authors were involved with writing.

For this update, SD and RAM carried out searches and study selection. All review authors were involved with revising the text.

SL will be responsible for future updates.

DECLARATIONS OF INTEREST

SL none known.

SD none known.

RAM has received institutional grant support from RB relating to individual patient level analyses of trial data on ibuprofen in acute pain and the effects of food on drug absorption of analgesics (2013), and from Grünenthal relating to individual patient level analyses of trial data regarding tapentadol in osteoarthritis and back pain (2015). He has received honoraria for attending boards with Menarini concerning methods of analgesic trial design (2014), with Novartis (2014) about the design of network meta-analyses, and RB on understanding pharmacokinetics of drug uptake (2015).

SOURCES OF SUPPORT

Internal sources

- Oxford Pain Relief Trust, UK

  General institutional support

External sources

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

  Funding for administrative costs associated with editorial and peer review of the protocol
- International Headache Society, UK

  Funding for administrative costs associated with editorial and peer review of the original review in 2013

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For this update we have changed the title of the review to "Sumatriptan plus naproxen for the treatment of acute migraine attacks in adults" to help to distinguish reviews of interventions for treatment from those for prophylaxis, and in line with other reviews in headache. We have also added a 'Summary of findings' table.

After discussion with headache specialists and editorial staff, and in line with Cochrane recommendations, we decided before writing the 2013 review 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 8.

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 and robustness of the results.

We originally planned to carry out a sensitivity analysis for study quality (Oxford Quality Score of 2 versus 3 or more) and for migraine with and without aura. We were unable to do either analysis in the earlier review because all the included studies score 3 or more, and no studies provided separate data for participants with and without aura. We have removed these sensitivity analyses from this updated review because issues of methodological quality are now dealt with in the 'Risk of bias' assessment, and there were no additional relevant data for aura.

NOTES

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)

Acute Disease; Anti-Inflammatory Agents, Non-Steroidal [*therapeutic use]; Drug Combinations; Drug Therapy, Combination [methods]; Migraine Disorders [*drug therapy]; Naproxen [*therapeutic use]; Randomized Controlled Trials as Topic; Serotonin 5-HT1 Receptor Agonists [*therapeutic use]; Sumatriptan [*administration & dosage]

MeSH check words

Adult; Humans