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Sumatriptan (oral route of administration) for acute migraine attacks in adults (Review)

Derry CJ, Derry S, Moore RA

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Sumatriptan (oral route of administration) for acute migraine attacks in adults.
Cochrane Database of Systematic Reviews 2012, Issue 2. Art. No.: CD008615.
DOI: 10.1002/14651858.CD008615.pub2.

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[Intervention Review]

Sumatriptan (oral route of administration) for acute migraine attacks in adults

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

Citation: Derry CJ, Derry S, Moore RA. Sumatriptan (oral route of administration) for acute migraine attacks in adults. *Cochrane Database of Systematic Reviews* 2012, Issue 2. Art. No.: CD008615. DOI: 10.1002/14651858.CD008615.pub2.

ABSTRACT

Background

Migraine is a highly disabling condition for the individual and also has wide-reaching implications for society, healthcare services, and the economy. Sumatriptan is an abortive medication for migraine attacks, belonging to the triptan family.

Objectives

To determine the efficacy and tolerability of oral sumatriptan compared to placebo and other active interventions in the treatment of acute migraine attacks in adults.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, online databases, and reference lists for studies through 13 October 2011.

Selection criteria

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

Data collection and analysis

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

Main results

Sixty-one studies (37,250 participants) compared oral sumatriptan with placebo or an active comparator. Most of the data were for the 50 mg and 100 mg doses. Sumatriptan surpassed placebo for all efficacy outcomes. For sumatriptan 50 mg versus placebo the NNTs were 6.1, 7.5, and 4.0 for pain-free at two hours and headache relief at one and two hours, respectively. NNTs for sustained pain-free and sustained headache relief during the 24 hours postdose were 9.5 and 6.0, respectively. For sumatriptan 100 mg versus placebo the NNTs were 4.7, 6.8, 3.5, 6.5, and 5.2, respectively, for the same outcomes. Results for the 25 mg dose were similar to the 50 mg dose, while sumatriptan 100 mg was significantly better than 50 mg for pain-free and headache relief at two hours, and for sustained pain-free during 24 hours. Treating early, during the mild pain phase, gave significantly better NNTs for pain-free at two hours and sustained pain-free during 24 hours than did treating established attacks with moderate or severe pain intensity.

Relief of associated symptoms, including nausea, photophobia, and phonophobia, was greater with sumatriptan than with placebo, and use of rescue medication was lower with sumatriptan than with placebo. For the most part, adverse events were transient and mild and were more common with the sumatriptan than with placebo, with a clear dose response relationship (25 mg to 100 mg).

Sumatriptan was compared directly with a number of active treatments, including other triptans, paracetamol (acetaminophen), acetylsalicylic acid, non-steroidal anti-inflammatory drugs (NSAIDs), and ergotamine combinations.

Authors' conclusions

Oral sumatriptan is effective as an abortive treatment for migraine attacks, relieving pain, nausea, photophobia, phonophobia, and functional disability, but is associated with increased adverse events.

PLAIN LANGUAGE SUMMARY

Sumatriptan (oral route of administration) for acute migraine attacks in adults

Sumatriptan is one of the triptan family of drugs used to treat migraine attacks. It is widely available as an oral tablet. This review found that a single dose was effective in relieving migraine headache pain and associated symptoms of nausea, sensitivity to light, and sensitivity to sound. Pain was reduced from moderate or severe to no pain by two hours in about 3 in 10 people (32%) taking sumatriptan 100 mg, compared with about 1 in 10 (11%) taking placebo. Pain was reduced from moderate or severe to no worse than mild pain by two hours in 6 in 10 people (61%) taking sumatriptan 100 mg, compared with about 3 in 10 (32%) taking placebo. Almost a quarter (24%) of people taking sumatriptan 100 mg had freedom from pain at two hours which was sustained during 24 hours without the use of rescue medication, compared with fewer than 1 in 10 (8%) taking placebo. In addition to relieving headache pain, sumatriptan also relieved symptoms of nausea and sensitivity to light and sound by two hours in about half of those who took it, compared with about one-third of those taking placebo. Adverse events were mostly of short duration and mild or moderate in severity, and were experienced by about 4 in 10 (43%) of people taking sumatriptan 100 mg, and by 2 in 10 (23%) taking placebo. The 50 mg dose had slightly lower efficacy, but was associated with fewer adverse events. Treating attacks while pain was still mild was more effective than treating established attacks with moderate or severe pain intensity.

BACKGROUND

Description of the condition

Migraine is a common, disabling headache disorder, with considerable social and economic impact (Hazard 2009). Recent reviews found a one-year prevalence of 15% for adults in European countries (Stovner 2010) and 13% for all ages in the US (Victor 2010). 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. Migraine without aura is the most common subtype. It is characterised by attacks lasting 4 to 72 hours that are typically of moderate to severe pain intensity, unilateral, pulsating, aggravated by normal physical activity, and associated with nausea and/or photophobia and phonophobia. Migraine with aura is characterised by reversible focal neurological symptoms that develop over a period of 5 to 20 minutes and last for less than 60 minutes, followed by headache with the features of migraine without aura. In some cases the headache may lack migrainous features or be absent altogether (IHS 2004).

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

The significant impact of migraine with regard to pain, disability, social functioning, quality of relationships, emotional well-being, and general health (Edmeads 1993; Osterhaus 1994; Solomon 1997) results in a huge burden for the individual, health services, and society (Clarke 1996; Ferrari 1998; Hazard 2009; Hu 1999; Solomon 1997). The annual US economic burden relating to migraine, including missed days of work and lost productivity, is USD 14 billion (Hu 1999). Thus successful treatment of acute migraine attacks not only benefits patients by reducing their disability and improving health-related quality of life, but also reduces the need for healthcare resources and increases economic productivity (Jhingran 1996; Lofland 1999).

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, in 1991. It is available as a standard oral tablet, nasal spray, subcutaneous injection, and rectal suppository. It is available only by prescription in most countries, but in the UK packs of 2 x 50 mg oral tablets are available OTC as Imigran Recovery for individuals with previously diagnosed migraine. Generic (non-proprietary) formulations are also available for the standard tablets in many countries. The nasal spray, subcutaneous, and rectal formulations may be particularly useful for individuals who experience severe nausea or vomiting with their attacks. This review will investigate only oral sumatriptan. In the UK in 2010 there were over 910,000 prescriptions for sumatriptan, of which about 782,000 were for the oral formulation, with about two-thirds for the 50 mg tablet and one-third for the 100 mg tablet (PCA 2011); the majority of prescribing (96%) was for generic sumatriptan.

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

Sumatriptan is a 5-HT_1 agonist, selectively targeting the 5-HT (serotonin) 1B and 1D receptors. It has three putative mechanisms of therapeutic action (Ferrari 2002; Goadsby 2007):

- 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.

It is used for acute treatment, having no efficacy in preventing future attacks.

Why it is important to do this review

Sumatriptan was the first marketed triptan and is by far the most used triptan worldwide. Since it came off patent, generic formulations have greatly increased its availability, and sumatriptan has become the standard against which new acute migraine treatments are compared. An earlier Cochrane review of oral sumatriptan for acute migraine headaches searched for studies to the end of 2001 (McCrory 2003) and included comparisons with placebo, no intervention, other drug treatments, and behavioural or physical therapies. More studies have been published since that time and an update is needed to include and evaluate the data from these. We decided to include all routes of administration in the update, and to limit comparators to placebo and other pharmacological interventions. Owing to the very large amount of information now available, particularly for the oral formulation, we carried out separate reviews for each route of administration (Derry 2012a; Derry 2012b; Derry 2012c; Derry 2012d), together with an overview of all routes of administration (Derry (forthcoming)). These sumatriptan reviews form part of a larger series of reviews planned for acute treatments for migraine attacks.

OBJECTIVES

The objective of this review is to determine the efficacy and tolerability of oral sumatriptan compared to 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- and/or active-controlled studies using oral sumatriptan to treat a migraine headache episode. Studies had to have a minimum of 10 participants per treatment arm and report dichotomous data for at least one of the outcomes specified below. We accepted studies reporting treatment of consecutive headache episodes if outcomes for the first, or each, episode were reported separately. Cross-over studies were accepted if there was adequate washout (≥ 48 hours) between treatments.

Types of participants

Studies enrolled adults (at least 18 years of age) with migraine. We used the definition of migraine specified by the International Headache Society (IHS 1988; IHS 2004), although we accepted diagnostic criteria equivalent to those of IHS 1988 where a specific reference was not provided. There were no restrictions on migraine frequency, duration, or type (with or without aura). Participants taking stable prophylactic therapy to reduce migraine frequency were accepted; where reported, details on the prophylactic therapy prescribed or allowed are provided in the Characteristics of included studies table.

Types of interventions

We included studies in which self administered oral sumatriptan was used to treat a migraine headache episode. There were no restrictions on dose, dosing regimen (e.g. single dose versus optional second dose) or timing of the first dose in relation to headache intensity (e.g. taking the first dose when pain was of moderate or severe intensity versus when pain was only mild).

A placebo comparator is essential to demonstrate that sumatriptan is effective in this condition. Active-controlled trials without a placebo were considered 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 pain relief, no headache recurrence, rapid onset of pain relief, and no side effects as the four most important outcomes (Lipton 1999).

In view of these patient preferences and in line with the guidelines for controlled trials of drugs in migraine issued by the IHS (IHS 2000), we considered the following primary outcomes:

- pain-free at two hours, without the use of rescue medication;
- reduction in headache pain ('headache relief') at one and two hours (pain reduced from moderate or severe to none or mild without the use of rescue medication);
- sustained pain-free during the 24 hours postdose (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 postdose (headache relief at two hours, sustained for 24 hours, with no use of rescue medication or a second dose of study medication).

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

- pain intensity: four-point categorical scale, with wording equivalent to none, mild, moderate, and severe; or 100 mm visual analogue scale (VAS);
- pain relief: five-point categorical scale, with wording equivalent to none, a little, some, a lot, complete; or 100 mm VAS.

All included studies used one or more of these standard scales and reported outcomes as defined above.

We considered only data obtained directly from the patient.

Secondary outcomes

Secondary outcomes considered were:

- use of rescue medication;
- participants with any adverse event during the 24 hours postdose;
- participants with particular adverse events during the 24 hours postdose;
- withdrawals due to adverse events;
- headache-associated symptoms: relief and/or presence at two hours;
- functional disability: relief and/or presence at two hours.

Although recurrence of headache is perceived to be a problem with triptan medication, we chose not to analyse this outcome because of variation in the definition of 'recurrence' and poor reporting, such that it is often unclear whether the result is reported as a proportion of the whole treatment group or only of those who experienced headache relief at two hours. Furthermore, because recurrence is dependent upon first experiencing headache relief at two hours - an outcome that varies across different treatment groups - interpretation of the result is difficult. We believe that the outcome of sustained headache relief at 24 hours qualitatively provides the same information to patients, but in a more rigorous and intuitive way.

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) (2011, Issue 10);
- MEDLINE (via OVID) (to 13 October 2011);
- EMBASE (via OVID) (to 13 October 2011);
- Oxford Pain Relief Database (Jadad 1996a).

See Appendix 2, Appendix 3, and Appendix 4 for the search strategies for MEDLINE, EMBASE, and CENTRAL, respectively. There were no language restrictions.

Searching other resources

We searched reference lists of retrieved studies and review articles for additional studies. We also searched online databases of clinical trials (www.gsk-clinicalstudyregister.com and www.clinicaltrials.gov). We made a written request for information about both published and unpublished data from the manufacturer of sumatriptan (GlaxoSmithKline), and asked specifically for further details on a number of studies published only on their clinical trial database. We did not search grey literature and short abstracts.

Data collection and analysis

Selection of studies

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

Data extraction and management

Two review authors independently extracted data from included studies using a standard data extraction form. Disagreements were settled by discussion with a third review author. One author entered data into RevMan 5.1 (RevMan 2011).

Assessment of risk of bias in included studies

We assessed methodological quality using the Oxford Quality Score (Jadad 1996b).

The scale is used as follows:

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

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

We also completed a 'Risk of bias' table for each study, using assessments of random sequence generation, allocation concealment, blinding, and study size.

Measures of treatment effect

We used relative risk (or 'risk ratio', RR) to establish statistical difference. Numbers needed to treat (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 than with control (placebo or active) we used the term the number needed to treat to prevent one event (NNTp).
- When significantly more adverse outcomes occurred with sumatriptan compared with control (placebo or active) we used the term the number needed to harm or cause one event (NNH).

Unit of analysis issues

We accepted randomisation at the individual patient level only.

Dealing with missing data

The most likely source of missing data was in cross-over studies. Where this might be problematic (e.g. where data were missing for > 10% of participants), we used only first-period data where available. In all cases (cross-over or parallel-group) we proposed to comment if there were substantial missing data and perform sensitivity analysis if possible.

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).

Assessment of reporting biases

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

Data synthesis

We analysed studies using a single dose of sumatriptan 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). We calculated relative risk of benefit or harm with 95% confidence intervals (CIs) using a fixed-effect model (Morris 1995). We calculated NNT, NNTp, and NNH with 95% CIs using the pooled number of events by the method of Cook and Sackett (Cook 1995). A statistically significant difference from control was assumed when the 95% CI of the relative risk of benefit or harm did not include the number one.

We determined significant differences between NNT, NNTp, and NNH for different doses of active treatment, or between groups in the sensitivity analyses, using the z test (Tramer 1997).

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

Subgroup analysis and investigation of heterogeneity

We analysed different doses separately. We performed subgroup analysis for different formulations of the oral treatment.

Sensitivity analysis

We planned sensitivity analysis for study quality (Oxford Quality Score of 2 versus 3 or more) and for migraine type (with aura versus without aura). A minimum of two studies and 200 participants were required for any sensitivity analysis. Where studies allowed a second dose of study medication but did not report incidence of adverse events separately for participants taking a single dose only, we carried out sensitivity analysis, removing these data to determine any effect of multiple dosing.

RESULTS

Description of studies

Included studies

Sixty-one studies (58 publications) fulfilled the inclusion criteria for this review; 55 were published in full peer-reviewed journals (Banerjee 1992; Brandes 2007 Study 1 and Study 2; Bussone 2000; Carpay 2004; Cutler 1995; Dahlof 1991; Dahlof 2009; Diener 2004a; Diener 2004b; DKSMSG 1999; Dodick 2002; Dowson 2002; Ensink 1991; Freitag 2001; Gallagher 2000; Geraud 2000; Goadsby 1991; Goadsby 2000; Goldstein 1998; Goldstein 2005; Gruffyd-Jones 2001; Havanka 2000; Ishkanian 2007; Jelinski 2006; Kaniecki 2006; Kolodny 2004; Kudrow 2005; Latere 1991; Lines 2001; Lipton 2000; Mathew 2003; Myllyla 1998; Nappi 1994; Nett 2003; Patten 1991; Pfaffenrath 1998; Pini 1995; Pini 1999; Sandrini 2002; Sandrini 2007; Sargent 1995; Savani 1999; Schulman 2003; Sheftell 2005 Study 1 and Study 2; Smith 2005; Spierings 2001; Tfelt-Hansen 1995; Tfelt-Hansen 1998; Tfelt-Hansen 2006; Thomson 1992; Visser 1996; Winner 2003 Study 1 and Study 2), five were available as Results Summaries on the manufacturer's website (GL/MIG/001/92; GL/MIG/001A/92; GL/MIG/002; GL/MIG/002A; GL/MIG/009), and one was a clinical trial report provided by the manufacturer (160-104). These studies provided data on 37,250 participants.

All of the included studies recruited adult participants only, with the majority (46/61) recruiting participants between 18 and 65 years of age (mean ages ranged from 33 to 43 years), and the remainder ranging from a 55 year maximum age to no upper limit on age. The majority of participants were female (70% to 100%) and suffering from migraine without aura (14% to 93%). All studies required participants to have had at least a 6- or 12-month history of migraine attacks (except one (160-104) which made no specific requirement for migraine history) meeting IHS (or equivalent) diagnostic criteria (IHS 1988; IHS 2004) before screening. Twenty-four studies required participants to discontinue any prophylactic medication at least two weeks before receiving study medication, while 13 studies allowed stable prophylactic medications (often excluding monoamine oxidase inhibitors, methysergide, and ergotamine or ergotamine-containing medications), and the remaining 24 studies did not report on prophylaxis. Twenty-two studies restricted participants from taking study medication within a defined time period of other acute migraine medications. This was most often 24 hours for any opiate, ergotamine, or triptan use, and six hours for any simple analgesics or antiemetics. The majority of the studies did not report on restricted acute migraine medications.

Participants were generally excluded for: pregnancy or breast-feeding; inadequate contraception; confirmed or suspected cardiovascular or cerebrovascular disease (particularly history of ischaemic heart disease); uncontrolled hypertension (diastolic ≥ 95 mmHg or systolic ≥ 160 mmHg); current or past drug abuse; psychiatric illness; epilepsy; hepatic disease; Raynaud's syndrome; and/or opthalmoplegic, basilar, or hemiplegic migraine. In addition, nine studies excluded participants if they had previously taken sumatriptan, while four studies required participants to have experience of sumatriptan to be eligible.

The baseline headache intensity at which study medication was administered varied amongst the included studies. The majority (35/61) administered the study drug when migraine headache pain was of moderate or severe intensity, but 14 studies required that medication should be taken at the first recognised signs of migraine attack, and six studies explicitly required the migraine to still be in the mild pain phase when treated. Six studies did not report the baseline headache intensity at which study medication was administered. Those studies requiring that medication be taken at the first recognised signs of migraine attack but not explicitly requiring pain to still be mild were dominated by participants treating moderate or severe attacks and provided data based specifically on this population. Similarly, in those studies not reporting the baseline headache intensity required for treatment, the vast majority of participants had moderate or severe migraine attacks at the time of dosing, and data were provided specifically on those participants.

Most of the included studies used a parallel-group design (53/61), treating a single migraine attack (34/61). Of those studies treating multiple attacks, most treated either two or three separate attacks (7 and 15 studies, respectively). The response of headaches to study treatment was measured using a standard four-point pain intensity scale in all 61 studies. The majority of the studies (58/61) reported at least one IHS-preferred outcome (IHS 2000); three studies reported only secondary outcomes. Just over half of the studies (31/61) offered participants the option of a second dose of study medication if either the initial response had been inadequate, or the participant experienced recurrence (defined as a relapse of moderate or severe intensity headache after an initial response) (14 studies); or to treat recurrence alone (17 studies). All studies but one reported allowing rescue medication if the response to study treatment was insufficient after a defined time period. Forty-two studies allowed some form of rescue medication after two hours, and 18 studies allowed it after four hours (one study reported allowing rescue medication but did not report at what time). In some cases rescue medication was available to treat recurrence as well as inadequate response, but most studies did not address this question specifically.

Twenty-four studies used only a placebo comparator, 13 studies used only active comparators, and 24 used both active and placebo comparators. The 61 studies reported on 57 different treatment comparisons.

- Sumatriptan 25 mg versus placebo (160-104; Cutler 1995; Goldstein 1998; Kolodny 2004; Pfaffenrath 1998; Sargent 1995).
- Sumatriptan 25 mg versus isometheptene mucate + dichloralphenazone + acetaminophen (Freitag 2001).
- Sumatriptan 25 mg versus zolmitriptan 2.5 mg (Gallagher 2000).
- Sumatriptan 25 mg versus zolmitriptan 5 mg (Gallagher 2000).
- Sumatriptan 25 mg versus rizatriptan 5 mg (Goldstein 1998; Kolodny 2004).
- Sumatriptan 25 mg versus rizatriptan 10 mg (Goldstein 1998; Kolodny 2004).
- Sumatriptan 25 mg versus eletriptan 40 mg (160-104).
- Sumatriptan 25 mg versus eletriptan 80 mg (160-104).
- Sumatriptan 50 mg versus placebo (160-104; Bussone 2000; Carpay 2004; Cutler 1995; Dahlof 2009; Diener 2004a; Diener 2004b; Goldstein 1998; Goldstein 2005; Ishkanian 2007; Jelinski 2006; Kolodny 2004; Kudrow 2005; Lines 2001; Lipton 2000; Nett 2003; Pfaffenrath 1998; Pini 1999; Sandrini 2002; Sargent 1995; Savani 1999; Sheftell 2005 Study 1 and Study 2; Smith 2005; Tfelt-Hansen 2006; Winner 2003 Study 1 and Study 2).
- Sumatriptan 50 mg versus tonabersat 20 mg (Dahlof 2009).
- Sumatriptan 50 mg versus tonabersat 40 mg (Dahlof 2009).
- Sumatriptan 50 mg versus effervescent acetylsalicylic acid (ASA) 1000 mg (Diener 2004a; Diener 2004b).
- Sumatriptan 50 mg versus ibuprofen 400 mg (Diener 2004b).
- Sumatriptan 50 mg versus zolmitriptan 2.5 mg (Gallagher 2000; Gruffyd-Jones 2001).
- Sumatriptan 50 mg versus zolmitriptan 5 mg (Gallagher 2000; Gruffyd-Jones 2001).
- Sumatriptan 50 mg versus rizatriptan 5 mg (Goldstein 1998; Kolodny 2004; Lines 2001).
- Sumatriptan 50 mg versus rizatriptan 10 mg (Goldstein 1998; Kolodny 2004).
- Sumatriptan 50 mg versus paracetamol (acetaminophen) 1000 mg + aspirin 1000 mg + caffeine 260 mg (Goldstein 2005).
- Sumatriptan 50 mg versus valdecoxib 20 mg (Kudrow 2005).
- Sumatriptan 50 mg versus valdecoxib 40 mg (Kudrow 2005).
- Sumatriptan 50 mg versus eletriptan 40 mg (160-104; Sandrini 2002).
- Sumatriptan 50 mg versus eletriptan 80 mg (160-104; Sandrini 2002).
- Sumatriptan 50 mg versus indomethacin 25 mg + prochlorperazine 2 mg + caffeine 75 mg (Indoprocaf) (Sandrini 2007).
- Sumatriptan 50 mg versus sumatriptan 50 mg + metoclopramide 10 mg (Schulman 2003).
- Sumatriptan 50 mg versus sumatriptan 50 mg + naproxen 500 mg (Smith 2005).
- Sumatriptan 50 mg versus naproxen 500 mg (Smith 2005).
- Sumatriptan 50 mg versus almotriptan 12.5 mg (Spierings 2001).
- Sumatriptan 85 mg versus placebo (Brandes 2007 Study 1 and Study 2).
- Sumatriptan 85 mg versus sumatriptan 85 mg + naproxen 500 mg (Brandes 2007 Study 1 and Study 2).
- Sumatriptan 85 mg versus naproxen 500 mg (Brandes 2007 Study 1 and Study 2).
- Sumatriptan 100 mg versus placebo (Carpay 2004; Cutler 1995; Dahlof 1991; DKSMSG 1999; Dodick 2002; Dowson 2002; Ensink 1991; Geraud 2000; Goadsby 1991; Goadsby 2000; Havanka 2000; Jelinski 2006; Kaniecki 2006; Mathew 2003; Myllyla 1998; Nappi 1994; Nett 2003; Patten 1991; Pfaffenrath 1998; Pini 1995; Sandrini 2002; Sargent 1995; Sheftell 2005 Study 1 and Study 2; Tfelt-Hansen 1995; Tfelt-Hansen 1998; Visser 1996; Winner 2003 Study 1 and Study 2).
- Sumatriptan 100 mg versus diclofenac potassium 50 mg (DKSMSG 1999).
- Sumatriptan 100 mg versus diclofenac potassium 100 mg (DKSMSG 1999).
- Sumatriptan 100 mg versus almotriptan 12.5 mg (Dodick 2002; Dowson 2002).
- Sumatriptan 100 mg versus almotriptan 25 mg (Dowson 2002).
- Sumatriptan 100 mg versus zolmitriptan 5 mg (Geraud 2000).
- Sumatriptan 100 mg versus paracetamol 1000 mg + metoclopramide (MCP) 10 mg (GL/MIG/001/92; GL/MIG/001A/92).
- Sumatriptan 100 mg versus buclizine hydrochloride 12.5 mg + paracetamol 1000 mg + codeine phosphate 16 mg (Migraleve) (GL/MIG/002; GL/MIG/002A).
- Sumatriptan 100 mg versus ergotamine tartrate 2 mg + cyclizine hydrochloride 50 mg + caffeine hydrate 100 mg (Migril) (GL/MIG/009).
- Sumatriptan 100 mg versus eletriptan 20 mg (Goadsby 2000).
- Sumatriptan 100 mg versus eletriptan 40 mg (Goadsby 2000; Mathew 2003; Sandrini 2002).
- Sumatriptan 100 mg versus eletriptan 80 mg (Goadsby 2000; Sandrini 2002).
- Sumatriptan 100 mg versus naratriptan 1 mg (Havanka 2000).
- Sumatriptan 100 mg versus naratriptan 2.5 mg (Havanka 2000).
- Sumatriptan 100 mg versus naratriptan 5 mg (Havanka 2000).
- Sumatriptan 100 mg versus naratriptan 7.5 mg (Havanka 2000).
- Sumatriptan 100 mg versus naratriptan 10 mg (Havanka 2000).
- Sumatriptan 100 mg versus ergotamine tartrate 2 mg + caffeine 200 mg (Cafergot) (Latere 1991).
- Sumatriptan 100 mg versus tolfenamic acid 200 mg (Myllyla 1998).
- Sumatriptan 100 mg versus rizatriptan 5 mg (Tfelt-Hansen 1998).
- Sumatriptan 100 mg versus rizatriptan 10 mg (Tfelt-Hansen 1998; Visser 1996).
- Sumatriptan 100 mg versus rizatriptan 20 mg (Visser 1996).
- Sumatriptan 100 mg versus rizatriptan 40 mg (Visser 1996).
- Sumatriptan 100 mg versus acetylsalicylic acid (ASA) 900 mg + metoclopramide (MCP) 10 mg (Tfelt-Hansen 1995; Thomson 1992).
- Sumatriptan 200 mg versus placebo (Banerjee 1992; Dahlof 1991; Patten 1991).
- Sumatriptan 300 mg versus placebo (Dahlof 1991; Patten 1991).

In total, 2111 participants were treated with sumatriptan 25 mg, 8081 with sumatriptan 50 mg, 849 with sumatriptan 85 mg, 8094 with sumatriptan 100 mg, 460 with sumatriptan 200 mg, 454 with sumatriptan 300 mg, 7016 with placebo, 1103 with naproxen, 855 with sumatriptan 85 mg + naproxen 500 mg, 251 with sumatriptan 50 mg + naproxen 500 mg, 131 with diclofenac potassium 50

mg, 122 with diclofenac potassium 100 mg, 134 with tonabersat 20 mg, 137 with tonabersat 40 mg, 369 with effervescent ASA 1000 mg, 212 with ibuprofen 400 mg, 958 with almotriptan 12.5 mg, 191 with almotriptan 25 mg, 65 with isometheptene mucate + dichloralphenazone + acetaminophen, 878 with zolmitriptan 2.5 mg, 1395 with zolmitriptan 5 mg, 675 with paracetamol 100 mg + MCP 10 mg, 710 with buclizine hydrochloride 12.5 mg + paracetamol 1000 mg + codeine phosphate 16 mg, 258 with ergotamine tartrate 2 mg + cyclizine hydrochloride 50 mg + caffeine hydrate 100 mg, 144 with eletriptan 20 mg, 1317 with eletriptan 40 mg, 485 with eletriptan 80 mg, 1606 with rizatriptan 5 mg, 1590 with rizatriptan 10 mg, 82 with rizatriptan 20 mg, 121 with rizatriptan 40 mg, 69 with acetaminophen 1000 mg + aspirin 1000 mg + caffeine 260 mg, 85 with naratriptan 1 mg, 87 with naratriptan 2.5 mg, 93 with naratriptan 5 mg, 93 with naratriptan 7.5 mg, 96 with naratriptan 10 mg, 137 with valdecoxib 20 mg, 152 with valdecoxib 40 mg, 289 with ergotamine tartrate 2 mg + caffeine 200 mg, 47 with tolfenamic acid 200 mg, 142 with indomethacin 25 mg + prochlorperazine 2 mg + caffeine 75 mg, 16 with sumatriptan 50 mg + MCP 10 mg, and 320 with ASA 900 mg + MCP 10 mg.

Some studies were inconsistent in the treatment group denominators reported, so that the population varied slightly in size for different outcomes or at different time points. Where this variability was not explained in the text, the denominators were changed to match the treated efficacy population if this gave a more conservative estimate of the efficacy of the drug.

Of the 61 included studies, 38 were either directly supported by the manufacturers of sumatriptan (GlaxoSmithKline, Glaxo Wellcome, or Glaxo) and are therefore very likely to have used branded sumatriptan (Imigran or Imitrex), or specifically reported using branded sumatriptan. Only three of the included studies did not report involvement of any pharmaceutical company, and the remaining 20 studies were supported by a different pharmaceutical company. For these 23 studies it is unknown whether branded sumatriptan or the generic equivalent was used; many of them may have used encapsulated branded sumatriptan, which, it has been suggested, is subject to delayed bioavailability and, possibly, reduced efficacy. The effect of this, in this analysis, would be conservative.

Full details of included studies are provided in the Characteristics of included studies table.

Excluded studies

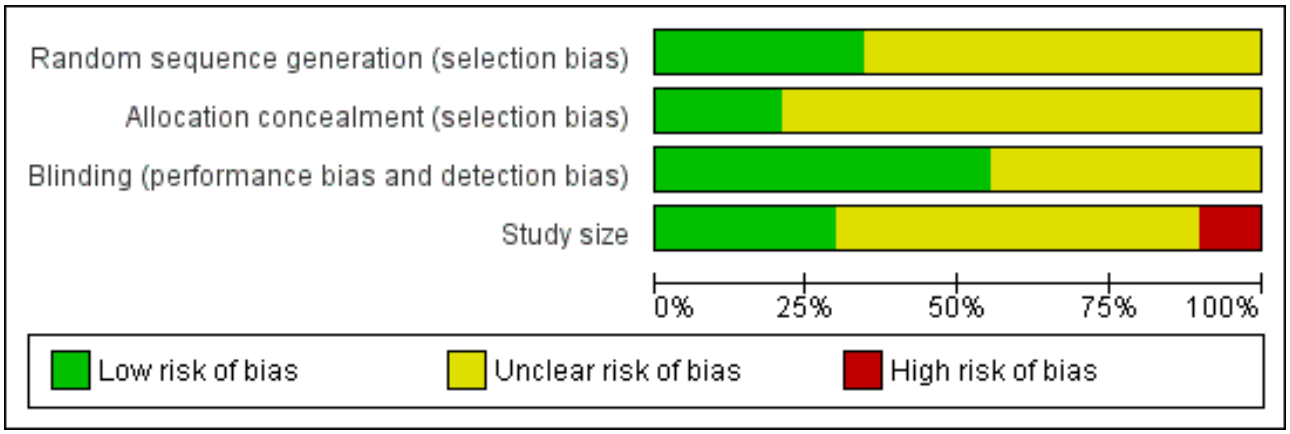
We excluded 23 studies after reading the full report (Cady 1994; Cady 2000; Centonze 1995; Colman 2001; Dowson 2000; Dowson 2005; Ferrari 1994; Gobel 2000; Landy 2004 (Study 1); Midelfart 1994; Padma 1998; Pradel 2005; Rapoport 1995; Rederich 1995; Salonen 1999; Savani 2001; Scott 1996; Sramek 1999; SUMA4014; Tepper 2006; Tfelt-Hansen 2000; Wells 2001; Wells 2003). The reasons for these exclusions are provided in the Characteristics of excluded studies table.

Risk of bias in included studies

Included studies were all randomised and double-blind. The majority of the studies provided information about withdrawals and dropouts, although 18 studies either made no statement about withdrawals or did not give an adequate explantation for differing treatment group denominators. The reliability of the trials was determined using the Oxford Quality Scale. Thirteen studies scored 5 of 5 on the scale, 19 studies scored 4 of 5, 15 studies scored 3 of 5, and 11 studies scored 2 of 5. Points were lost due to inadequate description of the methods of randomisation or double-blinding, and also lack of information about withdrawals and dropouts. Details are provided in the Characteristics of included studies table.

In addition, we created a 'Risk of bias' table which considered random sequence generation, allocation concealment, blinding, and study size (Figure 1). No studies were considered to be at high risk of bias from random sequence generation, allocation concealment, or blinding. Six studies (Banerjee 1992; Goldstein 2005; Myllyla 1998; Sargent 1995; Schulman 2003; Tfelt-Hansen 2006) did not include 50 or more participants in each treatment arm and were therefore considered to be at high risk of bias from their size.

Figure 1. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Effects of interventions

Details of results for efficacy in individual studies are provided in Appendix 5.

Although two very similar studies (Brandes 2007 Study 1 and Study 2) reported on the efficacy and safety of sumatriptan 85 mg verus placebo and active comparators, we chose not to analyse the data

for this dose of sumatriptan. Sumatriptan at a dose of 85 mg is not available outside of a combination treatment (sumatriptan plus naproxen) which is reviewed elsewhere (Law 2010), and falls between the two commonly used doses of sumatriptan, so does not contribute to our understanding of any potential dose response relationship.

Pain-free at two hours

Sumatriptan 25 mg versus placebo

Three studies (1108 participants) in participants with moderate or severe baseline pain provided data (160-104; Cutler 1995; Goldstein 1998).

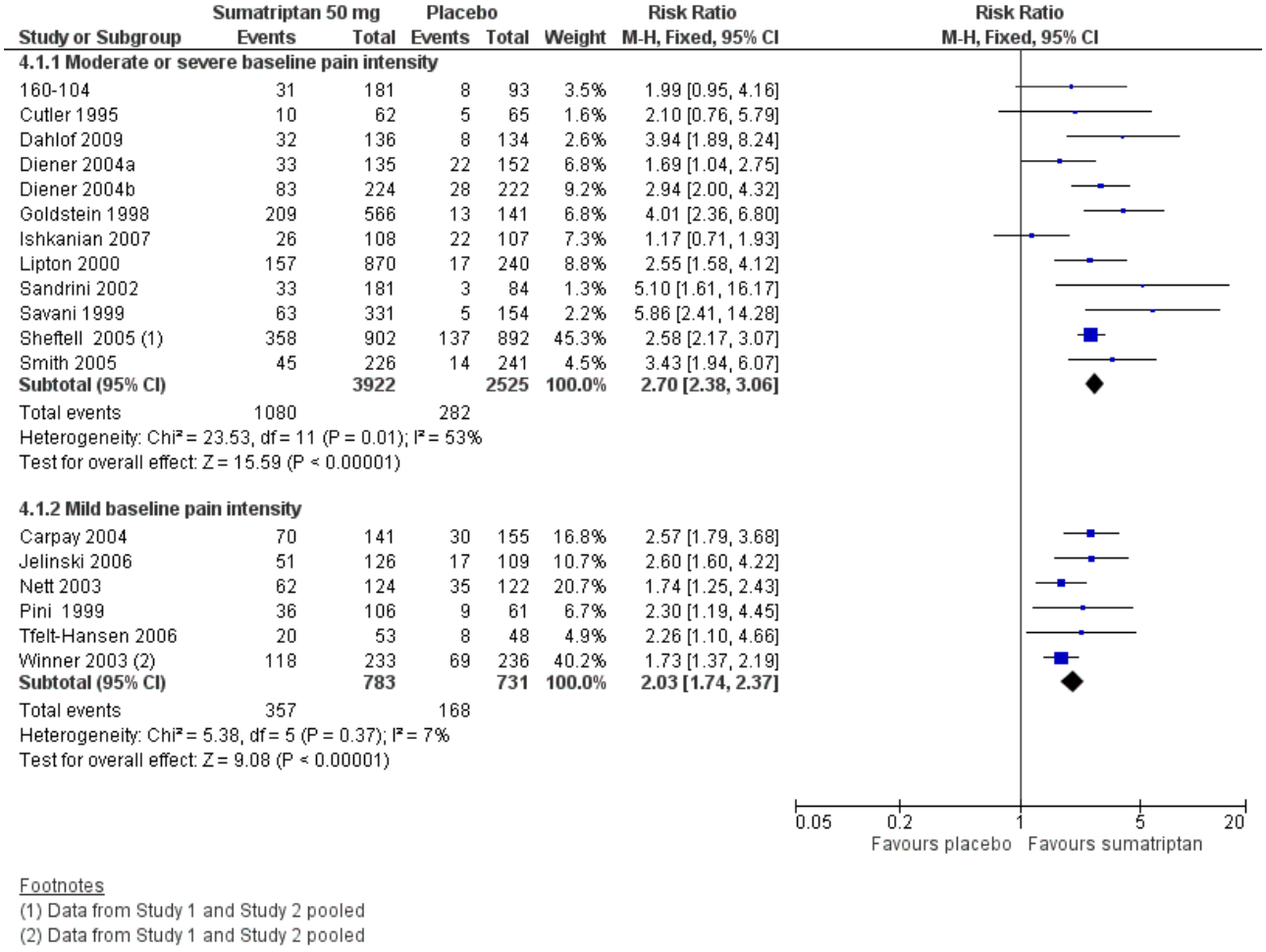
- The proportion of participants pain-free at two hours with sumatriptan 25 mg was 25% (201/809; range 16% to 28%).
- The proportion of participants pain-free at two hours with placebo was 9% (26/299; range 8% to 9%).
- The relative benefit of treatment compared with placebo was 2.7 (1.8 to 4.0; Analysis 1.1); the NNT was 6.2 (4.9 to 8.5).

Sumatriptan 50 mg versus placebo

Thirteen studies (6447 participants) in participants with moderate or severe baseline pain intensity provided data (160-104; Cutler 1995; Dahlof 2009; Diener 2004a; Diener 2004b; Goldstein 1998; Ishkanian 2007; Lipton 2000; Sandrini 2002; Savani 1999; Sheftell 2005 Study 1 and Study 2; Smith 2005).

- The proportion of participants pain-free at two hours with sumatriptan 50 mg was 28% (1080/3922; range 16% to 40%).
- The proportion of participants pain-free at two hours with placebo was 11% (282/2525; range 3% to 21%).
- The relative benefit of treatment compared with placebo was 2.7 (2.4 to 3.1; Analysis 4.1; Figure 2); the NNT was 6.1 (5.5 to 6.9).

Figure 2. Forest plot of comparison: 4 Oral sumatriptan 50 mg versus placebo, outcome: 4.1 Pain-free at 2 h.



Footnotes
(1) Data from Study 1 and Study 2 pooled
(2) Data from Study 1 and Study 2 pooled

Seven studies (1514 participants) in participants with mild baseline pain intensity provided data (Carpay 2004; Jelinski 2006; Nett 2003; Pini 1999; Tfelt-Hansen 2006; Winner 2003 Study 1 and Study 2).

- The proportion of participants pain-free at two hours with sumatriptan 50 mg was 46% (357/783; range 34% to 51%).
- The proportion of participants pain-free at two hours with placebo was 23% (168/731; range 15% to 29%).
- The relative benefit of treatment compared with placebo was 2.0 (1.7 to 2.4; Analysis 4.1); the NNT was 4.4 (3.8 to 5.7).

Treating early, while headache was still in the mild pain phase was significantly more effective than treating established moderate or severe headache pain (z = 2.283; P = 0.023; see Summary of results B).

Sumatriptan 100 mg versus placebo

Sixteen studies (6571 participants) in participants with moderate or severe baseline pain intensity provided data (Cutler 1995; Dodick 2002; Dowson 2002; Ensink 1991; Geraud 2000; Goadsby 2000; Kaniecki 2006; Mathew 2003; Myllyla 1998; Nappi 1994; Sandrini 2002; Sheftell 2005 Study 1 and Study 2; Tfelt-Hansen 1995; Tfelt-Hansen 1998; Visser 1996).

- The proportion of participants pain-free at two hours with sumatriptan 100 mg was 32% (1291/4017; range 17% to 50%).
- The proportion of participants pain-free at two hours with placebo was 11% (272/2554; range 4% to 16%).
- The relative benefit of treatment compared with placebo was 3.2 (2.8 to 3.6; Analysis 12.1); the NNT was 4.7 (4.3 to 5.1).

Sumatriptan 100 mg was significantly more effective than sumatriptan 50 mg in participants with moderate or severe baseline pain intensity (z = 3.451; P = 0.0007; see Summary of results B).

Five studies (1240 participants) in participants with mild baseline pain intensity provided data (Carpay 2004; Jelinski 2006; Nett 2003; Winner 2003 Study 1 and Study 2).

- The proportion of participants pain-free at two hours with sumatriptan 100 mg was 58% (358/618; range 50% to 64%).
- The proportion of participants pain-free at two hours with placebo was 24% (151/622; range 16% to 29%).
- The relative benefit of treatment compared with placebo was 2.4 (2.1 to 2.8; Analysis 12.1); the NNT was 3.0 (2.6 to 3.5).

Treating early, while headache was still in the mild pain phase was significantly more effective than treating established moderate or severe headache pain (z = 4.351; P < 0.00006).

Sumatriptan 100 mg was significantly more effective than sumatriptan 50 mg in participants with mild baseline pain intensity (z = 3.124; P = 0.002; see Summary of results B).

Sumatriptan 25 mg versus rizatriptan 5 mg

Two studies (2210 participants) in participants with moderate or severe baseline pain provided data (Goldstein 1998; Kolodny 2004).

- The proportion of participants pain-free at two hours with sumatriptan 25 mg was 28% (310/1117; range 27% to 28%).
- The proportion of participants pain-free at two hours with rizatriptan 5 mg was 33% (363/1093; range 33% to 33%).
- The relative benefit of sumatriptan compared with rizatriptan was 0.84 (0.74 to 0.95; Analysis 2.1); the NNT was 18 (11 to 62) in favour of rizatriptan.

Sumatriptan 25 mg versus rizatriptan 10 mg

Two studies (2231 participants) in participants with moderate or severe baseline pain provided data (Goldstein 1998; Kolodny 2004).

- The proportion of participants pain-free at two hours with sumatriptan 25 mg was 28% (310/1117; range 27% to 28%).
- The proportion of participants pain-free at two hours with rizatriptan 10 mg was 39% (440/1114; range 38% to 41%).
- The relative benefit of sumatriptan compared with rizatriptan was 0.70 (0.62 to 0.79; Analysis 3.1); the NNT was 8.5 (6.4 to 13) in favour of rizatriptan.

Sumatriptan 50 mg versus effervescent acetylsalicylic acid 1000 mg

Two studies (726 participants) in participants with moderate or severe baseline pain provided data (Diener 2004a; Diener 2004b).

- The proportion of participants pain-free at two hours with sumatriptan 50 mg was 32% (116/359; range 24% to 37%).
- The proportion of participants pain-free at two hours with effervescent ASA 1000 mg was 26% (97/367; range 25% to 27%).
- The relative benefit of sumatriptan compared with effervescent ASA was 1.2 (0.97 to 1.5; Analysis 5.1); there was no significant difference between treatments.

Sumatriptan 50 mg versus rizatriptan 5 mg

Two studies (2209 participants) provided data in participants with moderate or severe baseline pain (Goldstein 1998; Kolodny 2004).

- The proportion of participants pain-free at two hours with sumatriptan 50 mg was 35% (394/1116; range 34% to 37%).
- The proportion of participants pain-free at two hours with rizatriptan 5 mg was 33% (363/1093; range 33% to 33%).
- The relative benefit of sumatriptan compared with rizatriptan was 1.1 (0.95 to 1.2; Analysis 8.1); there was no significant difference between treatments.

Sumatriptan 50 mg versus rizatriptan 10 mg

Two studies (2230 participants) in participants with moderate or severe baseline pain provided data (Goldstein 1998; Kolodny 2004).

- The proportion of participants pain-free at two hours with sumatriptan 50 mg was 35% (394/1116; range 34% to 37%).
- The proportion of participants pain-free at two hours with rizatriptan 10 mg was 39% (440/1114; range 38% to 41%).
- The relative benefit of sumatriptan compared with rizatriptan was 0.89 (0.80 to 1.0; Analysis 9.1); there was no significant difference between treatments.

Sumatriptan 50 mg versus eletriptan 40 mg

Two studies (721 participants) in participants with moderate or severe baseline pain provided data (160-104; Sandrini 2002).

- The proportion of participants pain-free at two hours with sumatriptan 50 mg was 18% (64/362; range 17% to 18%).
- The proportion of participants pain-free at two hours with eletriptan 40 mg was 24% (86/359; range 18% to 30%).
- The relative benefit of sumatriptan compared with eletriptan was 0.74 (0.55 to 0.98; Analysis 10.1); the NNT was 16 (8.2 to 270) in favour of eletriptan.

Sumatriptan 50 mg versus eletriptan 80 mg

Two studies (706 participants) in participants with moderate or severe baseline pain provided data (160-104; Sandrini 2002).

- The proportion of participants pain-free at two hours with sumatriptan 50 mg was 18% (64/362; range 17% to 18%).
- The proportion of participants pain-free at two hours with eletriptan 40 mg was 30% (104/344; range 25% to 36%).
- The relative benefit of sumatriptan compared with eletriptan was 0.58 (0.44 to 0.76; Analysis 11.1); the NNT was 8.0 (5.3 to 16) in favour of eletriptan.

Sumatriptan 100 mg versus eletriptan 40 mg

Three studies (2263 participants) in participants with moderate or severe baseline pain provided data (Goadsby 2000; Mathew 2003; Sandrini 2002).

- The proportion of participants pain-free at two hours with sumatriptan 100 mg was 24% (271/1130; range 17% to 26%).
- The proportion of participants pain-free at two hours with eletriptan 40 mg was 32% (366/1133; range 25% to 34%).
- The relative benefit of sumatriptan compared with eletriptan was 0.74 (0.65 to 0.85; Analysis 13.1); the NNT was 12 (8.3 to 22) in favour of eletriptan.

Sumatriptan 100 mg versus eletriptan 80 mg

Two studies (604 participants) in participants with moderate or severe baseline pain provided data (Goadsby 2000; Sandrini 2002).

- The proportion of participants pain-free at two hours with sumatriptan 100 mg was 18% (55/299; range 17% to 20%).
- The proportion of participants pain-free at two hours with eletriptan 80 mg was 34% (103/305; range 31% to 36%).
- The relative benefit of sumatriptan compared with eletriptan was 0.54 (0.41 to 0.72; Analysis 14.1); the NNT was 6.5 (4.5 to 12) in favour of eletriptan.

Sumatriptan 100 mg versus rizatriptan 10 mg

Two studies (936 participants) in participants with moderate or severe baseline pain provided data (Tfelt-Hansen 1998; Visser 1996).

- The proportion of participants pain-free at two hours with sumatriptan 100 mg was 31% (143/460; range 22% to 33%).
- The proportion of participants pain-free at two hours with rizatriptan 10 mg was 37% (178/476; range 26% to 40%).
- The relative benefit of sumatriptan compared with rizatriptan was 0.82 (0.69 to 0.98; Analysis 15.1); the NNT was 16 (8.1 to 410) in favour of rizatriptan.

Sumatriptan 100 mg versus almotriptan 12.5 mg

Two studies (754 participants) in participants with moderate or severe baseline pain provided data (Dodick 2002; Dowson 2002).

- The proportion of participants pain-free at two hours with sumatriptan 100 mg was 33% (129/387; range 33% to 34%).
- The proportion of participants pain-free at two hours with almotriptan 12.5 mg was 28% (102/367; range 28% to 28%).
- The relative benefit of sumatriptan compared with almotriptan was 1.2 (0.97 to 1.5; Analysis 16.1); there was no significant difference between treatments.

Sumatriptan 100 mg versus acetylsalicylic acid 900 mg + metoclopramide 10 mg

Two studies (575 participants) in participants with moderate or severe baseline pain provided data (Tfelt-Hansen 1995; Thomson 1992).

- The proportion of participants pain-free at two hours with sumatriptan 100 mg was 26% (71/275; range 23% to 30%).
- The proportion of participants pain-free at two hours with ASA + MCP was 16% (48/300; range 12% to 21%).
- The relative benefit of sumatriptan compared with ASA + MCP was 1.6 (1.2 to 2.3; Analysis 18.1); the NNT was 10 (6.1 to 31).

Pain-free at one hour

Sumatriptan 50 mg versus placebo

Five studies (1735 participants) in participants with moderate or severe baseline pain intensity provided data (Dahlof 2009; Diener 2004a; Diener 2004b; Sandrini 2002; Smith 2005).

- The proportion of participants pain-free at one hour with sumatriptan 50 mg was 5% (45/902; range 4% to 6%).
- The proportion of participants pain-free at one hour with placebo was 2% (16/833; range 1% to 3%).
- The relative benefit of treatment compared with placebo was 2.6 (1.5 to 4.6; Analysis 4.2); the NNT was 33 (21 to 73).

Five studies (1246 participants) in participants with mild baseline pain intensity provided data (Carpay 2004; Jelinski 2006; Nett 2003; Winner 2003 Study 1 and Study 2).

- The proportion of participants pain-free at one hour with sumatriptan 50 mg was 26% (161/624; range 22% to 35%).
- The proportion of participants pain-free at one hour with placebo was 14% (87/622; range 7% to 19%).
- The relative benefit of treatment compared with placebo was 1.9 (1.5 to 2.4; Analysis 4.2); the NNT was 8.5 (6.2 to 13).

Sumatriptan 100 mg versus placebo

Six studies (3176 participants) in participants with moderate or severe baseline pain intensity provided data (Dowson 2002; Geraud 2000; Goadsby 2000; Mathew 2003; Sandrini 2002; Tfelt-Hansen 1998).

- The proportion of participants pain-free at one hour with sumatriptan 100 mg was 7% (158/2216; range 5% to 11%).
- The proportion of participants pain-free at one hour with placebo was 2% (15/960; range 0% to 2%).
- The relative benefit of treatment compared with placebo was 4.0 (2.3 to 6.8; Analysis 12.2); the NNT was 18 (15 to 24).

Five studies (1240 participants) in participants with mild baseline pain intensity provided data (Carpay 2004; Jelinski 2006; Nett 2003; Winner 2003 Study 1 and Study 2).

- The proportion of participants pain-free at one hour with sumatriptan 100 mg was 31% (189/618; range 24% to 43%).
- The proportion of participants pain-free at one hour with placebo was 14% (87/622; range 7% to 19%).
- The relative benefit of treatment compared with placebo was 2.2 (1.8 to 2.8; Analysis 12.2); the NNT was 6.0 (4.7 to 8.3).

Sumatriptan 50 mg versus effervescent acetylsalicylic acid 1000 mg

Two studies (726 participants) in participants with moderate or severe baseline pain intensity provided data (Diener 2004a; Diener 2004b).

- The proportion of participants pain-free at one hour with sumatriptan 50 mg was 5% (19/359).
- The proportion of participants pain-free at one hour with effervescent ASA 1000 mg was 5% (20/367; range 4% to 6%).
- The relative benefit of sumatriptan compared with effervescent ASA was 0.97 (0.53 to 1.8; Analysis 5.2); there was no significant difference between treatments.

Sumatriptan 100 mg versus eletriptan 40 mg

Three studies (2263 participants) in participants with moderate or severe baseline pain intensity provided data (Goadsby 2000; Mathew 2003; Sandrini 2002).

- The proportion of participants pain-free at one hour with sumatriptan 100 mg was 5% (59/1130; range 5% to 7%).
- The proportion of participants pain-free at one hour with eletriptan 40 mg was 7% (75/1133; range 6% to 7%).
- The relative benefit of sumatriptan compared with eletriptan was 0.79 (0.57 to 1.1; Analysis 13.2); there was no significant difference between treatments.

Sumatriptan 100 mg versus eletriptan 80 mg

Two studies (604 participants) in participants with moderate or severe baseline pain intensity provided data (Goadsby 2000; Sandrini 2002).

- The proportion of participants pain-free at one hour with sumatriptan 100 mg was 6% (19/299; range 5% to 7%).
- The proportion of participants pain-free at one hour with eletriptan 80 mg was 13% (40/305; range 12% to 14%).
- The relative benefit of sumatriptan compared with eletriptan was 0.48 (0.29 to 0.82; Analysis 14.2); the NNT was 15 (8.7 to 48) in favour of eletriptan.

Headache relief at one hour

All participants experiencing outcomes of headache relief must, by definition, have had moderate to severe pain at baseline.

Sumatriptan 25 mg versus placebo

Three studies (745 participants) provided data (160-104; Pfaffenrath 1998; Sargent 1995).

- The proportion of participants with headache relief at one hour with sumatriptan 25 mg was 27% (137/514; range 23% to 29%).
- The proportion of participants with headache relief at one hour with placebo was 16% (36/231; range 6% to 22%).
- The relative benefit of treatment compared with placebo was 1.6 (1.2 to 2.3; Analysis 1.2); the NNT was 9.0 (5.8 to 20).

Sumatriptan 50 mg versus placebo

Nine studies (2766 participants) provided data (160-104; Diener 2004a; Diener 2004b; Goldstein 2005; Pfaffenrath 1998; Sandrini 2002; Sargent 1995; Savani 1999; Smith 2005).

- The proportion of participants with headache relief at one hour with sumatriptan 50 mg was 27% (454/1655; range 13% to 50%).
- The proportion of participants with headache relief at one hour with placebo was 14% (157/1111; range 6% to 30%).
- The relative benefit of treatment compared with placebo was 1.8 (1.5 to 2.1; Analysis 4.3); the NNT was 7.5 (6.2 to 9.7).

Sumatriptan 100 mg versus placebo

Ten studies (3983 participants) provided data (Dowson 2002; Geraud 2000; Goadsby 2000; Havanka 2000; Mathew 2003; Pfaffenrath 1998; Sandrini 2002; Sargent 1995; Tfelt-Hansen 1998; Visser 1996).

- The proportion of participants with headache relief at one hour with sumatriptan 100 mg was 29% (795/2709; range 18% to 38%).
- The proportion of participants with headache relief at one hour with placebo was 15% (187/1274; range 6% to 29%).
- The relative benefit of treatment compared with placebo was 1.9 (1.6 to 2.2; Analysis 12.3); the NNT was 6.8 (5.8 to 8.3).

Sumatriptan 25 mg versus rizatriptan 5 mg

Two studies (2210 participants) provided data (Goldstein 1998; Kolodny 2004).

- The proportion of participants with headache relief at one hour with sumatriptan 25 mg was 34% (375/1117; range 33% to 34%).
- The proportion of participants with headache relief at one hour with rizatriptan 5 mg was 37% (404/1093; range 36% to 38%).
- The relative benefit of sumatriptan compared with rizatriptan was 0.91 (0.81 to 1.0; Analysis 2.2); the NNT was 29 (14 to 170) in favour of rizatriptan.

Sumatriptan 25 mg versus rizatriptan 10 mg

Two studies (2231 participants) provided data (Goldstein 1998; Kolodny 2004).

- The proportion of participants with headache relief at one hour with sumatriptan 25 mg was 34% (375/1117; range 33% to 34%).
- The proportion of participants with headache relief at one hour with rizatriptan 10 mg was 41% (456/1114; range 40% to 42%).
- The relative benefit of sumatriptan compared with rizatriptan was 0.82 (0.74 to 0.91; Analysis 3.2); the NNT was 14 (8.8 to 30) in favour of rizatriptan.

Sumatriptan 50 mg versus effervescent acetylsalicylic acid 1000 mg

Two studies (726 participants) provided data (Diener 2004a; Diener 2004b).

- The proportion of participants with headache relief at one hour with sumatriptan 50 mg was 24% (86/359).
- The proportion of participants with headache relief at one hour with effervescent ASA 1000 mg was 31% (113/367; range 25% to 34%).
- The relative benefit of sumatriptan compared with effervescent ASA was 0.78 (0.61 to 0.98; Analysis 5.3); the NNT was 15 (7.5 to 270) in favour of effervescent ASA.

Sumatriptan 50 mg versus zolmitriptan 2.5 mg

Two studies (1609 participants) provided data (Gallagher 2000; Gruffyd-Jones 2001).

- The proportion of participants with headache relief at one hour with sumatriptan 50 mg was 41% (330/814; range 35% to 44%).
- The proportion of participants with headache relief at one hour with zolmitriptan 2.5 mg was 40% (318/795; range 35% to 43%).
- The relative benefit of sumatriptan compared with zolmitriptan was 1.0 (0.90 to 1.1; Analysis 6.1); there was no significant difference between treatments.

Sumatriptan 50 mg versus zolmitriptan 5 mg

Two studies (1633 participants) provided data (Gallagher 2000; Gruffyd-Jones 2001).

- The proportion of participants with headache relief at one hour with sumatriptan 50 mg was 41% (330/814; range 35% to 44%).
- The proportion of participants with headache relief at one hour with zolmitriptan 5 mg was 39% (320/819; range 37% to 40%).
- The relative benefit of sumatriptan compared with zolmitriptan was 1.0 (0.90 to 1.2; Analysis 7.1); there was no significant difference between treatments.

Sumatriptan 50 mg versus rizatriptan 5 mg

Two studies (2209 participants) provided data (Goldstein 1998; Kolodny 2004).

- The proportion of participants with headache relief at one hour with sumatriptan 50 mg was 37% (409/1116; range 35% to 39%).
- The proportion of participants with headache relief at one hour with rizatriptan 5 mg was 37% (404/1093; range 36% to 38%).
- The relative benefit of sumatriptan compared with rizatriptan was 0.99 (0.89 to 1.1; Analysis 8.2); there was no significant difference between treatments.

Sumatriptan 50 mg versus rizatriptan 10 mg

Two studies (2230 participants) provided data (Goldstein 1998; Kolodny 2004).

- The proportion of participants with headache relief at one hour with sumatriptan 50 mg was 37% (409/1116; range 35% to 39%).
- The proportion of participants with headache relief at one hour with rizatriptan 10 mg was 41% (456/1114; range 40% to 42%).
- The relative benefit of sumatriptan compared with rizatriptan was 0.90 (0.81 to 1.0; Analysis 9.2); there was no significant difference between treatments.

Sumatriptan 50 mg versus eletriptan 40 mg

Two studies (721 participants) provided data (160-104; Sandrini 2002).

- The proportion of participants with headache relief at one hour with sumatriptan 50 mg was 25% (90/362; range 23% to 27%).
- The proportion of participants with headache relief at one hour with eletriptan 40 mg was 25% (90/359; range 21% to 30%).
- The relative benefit of sumatriptan compared with eletriptan was 0.99 (0.77 to 1.3; Analysis 10.2); there was no significant difference between treatments.

Sumatriptan 50 mg versus eletriptan 80 mg

Two studies (706 participants) provided data (160-104; Sandrini 2002).

- The proportion of participants with headache relief at one hour with sumatriptan 50 mg was 25% (90/362; range 23% to 27%).
- The proportion of participants with headache relief at one hour with eletriptan 80 mg was 35% (119/344; range 34% to 35%).
- The relative benefit of sumatriptan compared with eletriptan was 0.72 (0.57 to 0.91; Analysis 11.2); the NNT was 10 (6.1 to 33) in favour of eletriptan.

Sumatriptan 100 mg versus eletriptan 40 mg

Three studies (2263 participants) provided data (Goadsby 2000; Mathew 2003; Sandrini 2002).

- The proportion of participants with headache relief at one hour with sumatriptan 100 mg was 25% (282/1130; range 18% to 26%).
- The proportion of participants with headache relief at one hour with eletriptan 40 mg was 32% (368/1133; range 30% to 33%).
- The relative benefit of sumatriptan compared with eletriptan was 0.77 (0.67 to 0.88; Analysis 13.3); the NNT was 13 (8.9 to 26) in favour of eletriptan.

Sumatriptan 100 mg versus eletriptan 80 mg

Two studies (604 participants) provided data (Goadsby 2000; Sandrini 2002).

- The proportion of participants with headache relief at one hour with sumatriptan 100 mg was 23% (68/299; range 18% to 26%).
- The proportion of participants with headache relief at one hour with eletriptan 80 mg was 35% (106/305; range 34% to 35%).
- The relative benefit of sumatriptan compared with eletriptan was 0.65 (0.50 to 0.84; Analysis 14.3); the NNT was 8.3 (5.2 to 21) in favour of eletriptan.

Sumatriptan 100 mg versus rizatriptan 10 mg

Two studies (936 participants) provided data (Tfelt-Hansen 1998; Visser 1996).

- The proportion of participants with headache relief at one hour with sumatriptan 100 mg was 26% (120/460; range 24% to 27%).
- The proportion of participants with headache relief at one hour with rizatriptan 10 mg was 34% (163/476; range 25% to 36%).
- The relative benefit of sumatriptan compared with rizatriptan was 0.76 (0.62 to 0.92; Analysis 15.2); the NNT was 12 (7.1 to 43) in favour of rizatriptan.

Headache relief at two hours

All participants experiencing outcomes of headache relief must, by definition, have had moderate to severe pain at baseline.

Sumatriptan 25 mg versus placebo

Five studies (1580 participants) provided data (160-104; Cutler 1995; Goldstein 1998; Pfaffenrath 1998; Sargent 1995).

- The proportion of participants with headache relief at two hours with sumatriptan 25 mg was 56% (638/1143; range 49% to 62%).

- The proportion of participants with headache relief at two hours with placebo was 32% (140/437; range 17% to 38%).
- The relative benefit of treatment compared with placebo was 1.7 (1.4 to 1.9; Analysis 1.3); the NNT was 4.2 (3.5 to 5.4).

Sumatriptan 50 mg versus placebo

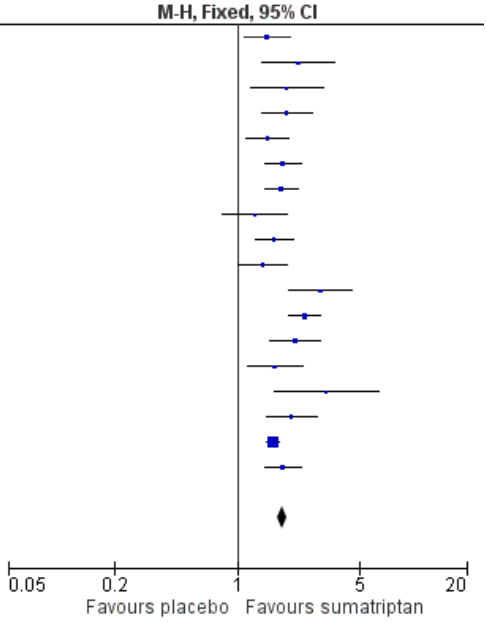
Nineteen studies (8102 participants) provided data (160-104; Bussone 2000; Cutler 1995; Dahlof 2009; Diener 2004a; Diener 2004b; Goldstein 1998; Goldstein 2005; Ishkanian 2007; Kudrow 2005; Lines 2001; Lipton 2000; Pfaffenrath 1998; Sandrini 2002; Sargent 1995; Savani 1999; Sheftell 2005 Study 1 and Study 2; Smith 2005).

- The proportion of participants with headache relief at two hours with sumatriptan 50 mg was 57% (2822/4955; range 42% to 69%).
- The proportion of participants with headache relief at two hours with placebo was 32% (1007/3147; range 17% to 52%).
- The relative benefit of treatment compared with placebo was 1.8 (1.7 to 1.9; Analysis 4.4; Figure 3); the NNT was 4.0 (3.7 to 4.4).

Figure 3. Forest plot of comparison: 4 Oral sumatriptan 50 mg versus placebo, outcome: 4.4 Headache relief at 2 h.

Study or Subgroup	Sumatriptan 50 mg Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
160-104	98	181	34	93	4.0%	1.48 [1.10, 2.00]
Bussone 2000	87	156	14	56	1.8%	2.23 [1.39, 3.59]
Cutler 1995	31	62	17	65	1.5%	1.91 [1.18, 3.08]
Dahlof 2009	70	136	36	134	3.2%	1.92 [1.39, 2.65]
Diener 2004a	66	135	50	152	4.2%	1.49 [1.12, 1.98]
Diener 2004b	125	224	68	222	6.0%	1.82 [1.45, 2.29]
Goldstein 1998	385	566	54	141	7.6%	1.78 [1.43, 2.21]
Goldstein 2005	30	46	14	27	1.6%	1.26 [0.83, 1.91]
Ishkanian 2007	75	108	46	107	4.1%	1.62 [1.26, 2.08]
Kudrow 2005	60	144	42	141	3.7%	1.40 [1.02, 1.92]
Lines 2001	239	356	18	80	2.6%	2.98 [1.97, 4.51]
Lipton 2000	409	870	82	420	9.8%	2.41 [1.96, 2.96]
Pfaffenrath 1998	180	285	27	91	3.6%	2.13 [1.53, 2.96]
Sandrini 2002	88	181	25	84	3.0%	1.63 [1.14, 2.34]
Sargent 1995	25	46	8	47	0.7%	3.19 [1.61, 6.33]
Savani 1999	140	331	32	154	3.9%	2.04 [1.46, 2.84]
Sheftell 2005 (1)	603	902	375	892	33.3%	1.59 [1.45, 1.74]
Smith 2005	111	226	65	241	5.6%	1.82 [1.42, 2.33]
Total (95% CI)		**4955**		**3147**	**100.0%**	**1.80 [1.70, 1.91]**
Total events	2822		1007			

Heterogeneity: Chi² = 35.64, df = 17 (P = 0.005); I² = 52%
Test for overall effect: Z = 19.83 (P < 0.00001)



Footnotes
(1) Data from Study 1 and Study 2 pooled

Sumatriptan 100 mg versus placebo

Twenty-one studies (7811 participants) provided data (Cutler 1995; Dahlof 1991; Dowson 2002; Ensink 1991; Geraud 2000; Goadsby 1991; Goadsby 2000; Havanka 2000; Kaniecki 2006; Mathew 2003; Myllyla 1998; Nappi 1994; Patten 1991; Pfaffenrath 1998; Sandrini 2002; Sargent 1995; Sheftell 2005 Study 1 and Study 2; Tfelt-Hansen 1995; Tfelt-Hansen 1998; Visser 1996).

- The proportion of participants with headache relief at two hours with sumatriptan 100 mg was 61% (2877/4751; range 46% to 79%).
- The proportion of participants with headache relief at two hours with placebo was 32% (967/3060; range 10% to 43%).
- The relative benefit of treatment compared with placebo was 1.9 (1.8 to 2.0; Analysis 12.4); the NNT was 3.5 (3.2 to 3.7).

Sumatriptan 100 mg was significantly more effective than sumatriptan 50 mg (z = 2.407; P = 0.016; see Summary of results B).

Sumatriptan 200 mg versus placebo

Three studies (749 participants) provided data (Banerjee 1992; Dahlof 1991; Patten 1991).

- The proportion of participants with headache relief at two hours with sumatriptan 200 mg was 72% (311/429; range 62% to 75%).
- The proportion of participants with headache relief at two hours with placebo was 26% (82/320; range 22% to 32%).
- The relative benefit of treatment compared with placebo was 2.8 (2.3 to 3.5; Analysis 19.1); the NNT was 2.1 (1.9 to 2.5).

Sumatriptan 200 mg was significantly more effective than sumatriptan 100 mg (z = 5.212; P < 0.00006).

Sumatriptan 300 mg versus placebo

Two studies (709 participants) provided data (Dahlof 1991; Patten 1991).

- The proportion of participants with headache relief at two hours with sumatriptan 300 mg was 67% (286/426; range 66% to 69%).

- The proportion of participants with headache relief at two hours with placebo was 25% (70/283; range 22% to 26%).
- The relative benefit of treatment compared with placebo was 2.7 (2.2 to 3.4; Analysis 20.1); the NNT was 2.4 (2.0 to 2.8).

Sumatriptan 25 mg versus rizatriptan 5 mg

Two studies (2210 participants) provided data (Goldstein 1998; Kolodny 2004).

- The proportion of participants with headache relief at two hours with sumatriptan 25 mg was 35% (386/1117; range 12% to 58%).
- The proportion of participants with headache relief at two hours with rizatriptan 5 mg was 67% (731/1093; range 66% to 68%).
- The relative benefit of sumatriptan compared with rizatriptan was 0.90 (0.84 to 0.95; Analysis 2.3); the NNT was 14 (9.1 to 34) in favour of rizatriptan.

Sumatriptan 25 mg versus rizatriptan 10 mg

Two studies (2231 participants) provided data (Goldstein 1998; Kolodny 2004).

- The proportion of participants with headache relief at two hours with sumatriptan 25 mg was 35% (386/1117; range 12% to 58%).
- The proportion of participants with headache relief at two hours with rizatriptan 10 mg was 70% (780/1114; range 68% to 72%).
- The relative benefit of sumatriptan compared with rizatriptan was 0.86 (0.80 to 0.91; Analysis 3.3); the NNT was 9.9 (7.1 to 16) in favour of rizatriptan.

Sumatriptan 50 mg versus effervescent acetylsalicylic acid 1000 mg

Two studies (726 participants) provided data (Diener 2004a; Diener 2004b).

- The proportion of participants with headache relief at two hours with sumatriptan 50 mg was 53% (191/359; range 49% to 56%).
- The proportion of participants with headache relief at two hours with effervescent ASA 1000 mg was 42% (153/367; range 25% to 52%).
- The relative benefit of sumatriptan compared with effervescent ASA was 1.3 (1.1 to 1.5; Analysis 5.4); the NNT was 8.7 (5.3 to 23).

Sumatriptan 50 mg versus zolmitriptan 2.5 mg

Two studies (1609 participants) provided data (Gallagher 2000; Gruffyd-Jones 2001).

- The proportion of participants with headache relief at two hours with sumatriptan 50 mg was 67% (543/814; range 59% to 71%).
- The proportion of participants with headache relief at two hours with zolmitriptan 2.5 mg was 66% (523/795; range 65% to 67%).
- The relative benefit of sumatriptan compared with zolmitriptan was 1.0 (0.95 to 1.1; Analysis 6.2); there was no significant difference between treatments.

Sumatriptan 50 mg versus zolmitriptan 5 mg

Two studies (1633 participants) provided data (Gallagher 2000; Gruffyd-Jones 2001).

- The proportion of participants with headache relief at two hours with sumatriptan 50 mg was 67% (543/814; range 59% to 71%).
- The proportion of participants with headache relief at two hours with zolmitriptan 5 mg was 66% (537/819; range 65% to 66%).
- The relative benefit of sumatriptan compared with zolmitriptan was 1.0 (0.95 to 1.1; Analysis 7.2); there was no significant difference between treatments.

Sumatriptan 50 mg versus rizatriptan 5 mg

Three studies (2911 participants) provided data (Goldstein 1998; Kolodny 2004; Lines 2001).

- The proportion of participants with headache relief at two hours with sumatriptan 50 mg was 65% (949/1469; range 62% to 67%).
- The proportion of participants with headache relief at two hours with rizatriptan 5 mg was 66% (951/1442; range 63% to 68%).
- The relative benefit of sumatriptan compared with rizatriptan was 0.98 (0.93 to 1.0; Analysis 8.3); there was no significant difference between treatments.

Sumatriptan 50 mg versus rizatriptan 10 mg

Two studies (2227 participants) provided data (Goldstein 1998; Kolodny 2004).

- The proportion of participants with headache relief at two hours with sumatriptan 50 mg was 64% (710/1113; range 62% to 66%).
- The proportion of participants with headache relief at two hours with rizatriptan 10 mg was 70% (780/1114; range 68% to 72%).
- The relative benefit of sumatriptan compared with rizatriptan was 0.91 (0.86 to 0.97; Analysis 9.3); the NNT was 16 (9.9 to 43) in favour of rizatriptan.

Sumatriptan 50 mg versus eletriptan 40 mg

Two studies (721 participants) provided data (160-104; Sandrini 2002).

- The proportion of participants with headache relief at two hours with sumatriptan 50 mg was 51% (186/362; range 49% to 54%).
- The proportion of participants with headache relief at two hours with eletriptan 40 mg was 60% (217/359; range 59% to 62%).
- The relative benefit of sumatriptan compared with eletriptan was 0.85 (0.75 to 0.97; Analysis 10.3); the NNT was 11 (6.1 to 54) in favour of eletriptan.

Sumatriptan 50 mg versus eletriptan 80 mg

Two studies (706 participants) provided data (160-104; Sandrini 2002).

- The proportion of participants with headache relief at two hours with sumatriptan 50 mg was 51% (186/362; range 49% to 54%).
- The proportion of participants with headache relief at two hours with eletriptan 80 mg was 66% (226/344; range 65% to 66%).
- The relative benefit of sumatriptan compared with eletriptan was 0.78 (0.69 to 0.89; Analysis 11.3); the NNT was 7.0 (4.7 to 14) in favour of eletriptan.

Sumatriptan 100 mg versus eletriptan 40 mg

Three studies (2263 participants) provided data (Goadsby 2000; Mathew 2003; Sandrini 2002).

- The proportion of participants with headache relief at two hours with sumatriptan 100 mg was 55% (622/1130; range 50% to 57%).
- The proportion of participants with headache relief at two hours with eletriptan 40 mg was 62% (706/1133; range 56% to 64%).
- The relative benefit of sumatriptan compared with eletriptan was 0.88 (0.82 to 0.95; Analysis 13.4); the NNT was 14 (8.9 to 31) in favour of eletriptan.

Sumatriptan 100 mg versus eletriptan 80 mg

Two studies (604 participants) provided data (Goadsby 2000; Sandrini 2002).

- The proportion of participants with headache relief at two hours with sumatriptan 100 mg was 51% (151/299; range 50% to 51%).
- The proportion of participants with headache relief at two hours with eletriptan 80 mg was 65% (198/305; range 65% to 65%).
- The relative benefit of sumatriptan compared with eletriptan was 0.78 (0.68 to 0.89; Analysis 14.4); the NNT was 6.9 (4.5 to 15) in favour of eletriptan.

Sumatriptan 100 mg versus paracetamol 1000 mg + metoclopramide 10 mg

Two studies (1035 participants) provided data (GL/MIG/001/92; GL/MIG/001A/92).

- The proportion of participants with headache relief at two hours with sumatriptan 100 mg was 45% (233/514; range 42% to 49%).
- The proportion of participants with headache relief at two hours with paracetamol 1000 mg + MCP 10 mg was 43% (225/521; range 41% to 45%).
- The relative benefit of sumatriptan compared with paracetamol + MCP was 1.1 (0.91 to 1.2; Analysis 17.1); there was no significant difference between the treatments.

Sumatriptan 100 mg versus acetylsalicylic acid 900 mg + metoclopramide 10 mg

Two studies (575 participants) provided data (Tfelt-Hansen 1995; Thomson 1992).

- The proportion of participants with headache relief at two hours with sumatriptan 100 mg was 50% (137/275; range 48% to 52%).
- The proportion of participants with headache relief at two hours with ASA 900 mg + MCP 10 mg was 46% (138/300; range 38% to 55%).
- The relative benefit of sumatriptan compared with ASA + MCP was 1.1 (0.92 to 1.3; Analysis 18.2); there was no significant difference between the treatments.

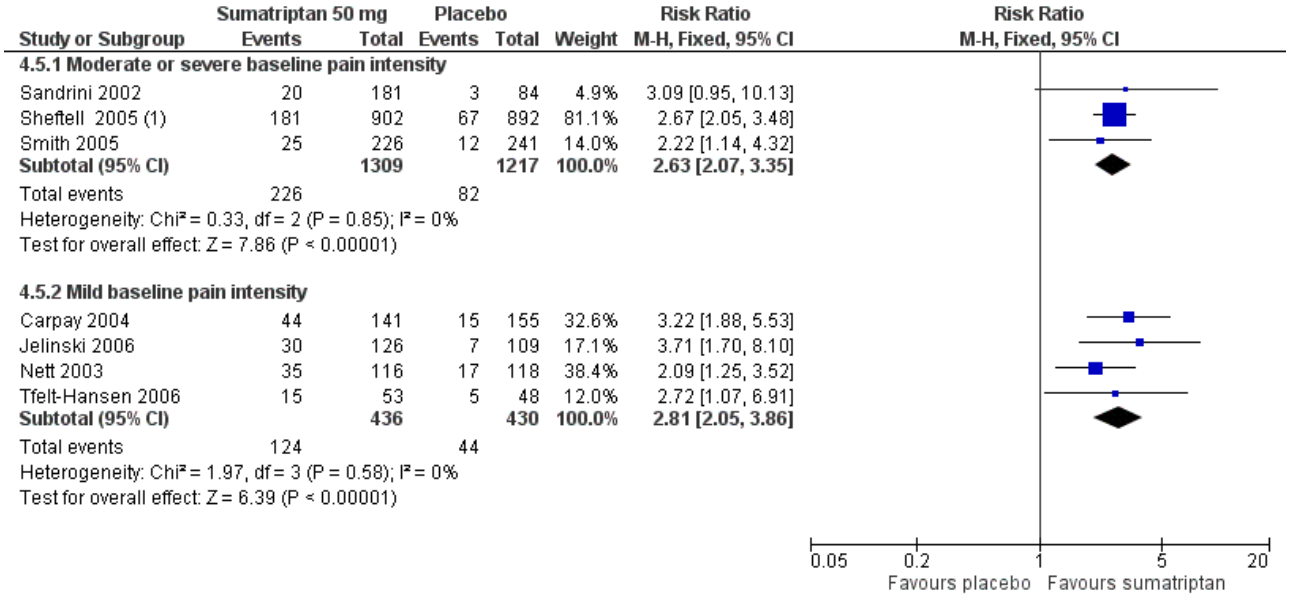
Sustained pain-free during the 24 hours postdose

Sumatriptan 50 mg versus placebo

Four studies (2526 participants) in participants with moderate or severe baseline pain intensity provided data (Sandrini 2002; Sheftell 2005 Study 1 and Study 2; Smith 2005).

- The proportion of participants with a 24-hour sustained pain-free response with sumatriptan 50 mg was 17% (226/1309; range 11% to 20%).
- The proportion of participants with a 24-hour sustained pain-free response with placebo was 7% (82/1217; range 4% to 8%).
- The relative benefit of treatment compared with placebo was 2.6 (2.1 to 3.4; Analysis 4.5; Figure 4); the NNT was 9.5 (7.7 to 12).

Figure 4. Forest plot of comparison: 4 Oral sumatriptan 50 mg versus placebo, outcome: 4.5 24 h sustained pain-free.



Footnotes
(1) Data from Study 1 and Study 2 pooled

Four studies (866 participants) in participants with mild baseline pain intensity provided data (Carpay 2004; Jelinski 2006; Nett 2003; Tfelt-Hansen 2006).

- The proportion of participants with a 24-hour sustained pain-free response with sumatriptan 50 mg was 28% (124/436; range 24% to 31%).
- The proportion of participants with a 24-hour sustained pain-free response with placebo was 10% (44/430; range 6% to 14%).
- The relative benefit of treatment compared with placebo was 2.8 (2.1 to 3.9; Analysis 4.5); the NNT was 5.5 (4.3 to 7.6).

Treating early, while headache was still in the mild pain phase was significantly more effective than treating established moderate or severe headache pain (z = 2.648; P = 0.008; see Summary of results B).

Sumatriptan 100 mg versus placebo

Six studies (2891 participants) in participants with moderate or severe baseline pain intensity provided data (Dodick 2002; Dowson 2002; Kaniecki 2006; Sandrini 2002; Sheftell 2005 Study 1 and Study 2).

- The proportion of participants with a 24-hour sustained pain-free response with sumatriptan 100 mg was 24% (374/1590; range 14% to 29%).
- The proportion of participants with a 24-hour sustained pain-free response with placebo was 8% (106/1301; range 4% to 17%).
- The relative benefit of treatment compared with placebo was 2.8 (2.4 to 3.5; Analysis 12.5); the NNT was 6.5 (5.6 to 7.8).

Sumatriptan 100 mg was significantly more effective than sumatriptan 50 mg in participants with moderate or severe baseline pain intensity (z = 2.663; P = 0.008; see Summary of results B).

Three studies (771 participants) in participants with mild baseline pain intensity provided data (Carpay 2004; Jelinski 2006; Nett 2003).

- The proportion of participants with a 24-hour sustained pain-free response with sumatriptan 100 mg was 33% (127/389; range 27% to 39%).
- The proportion of participants with a 24-hour sustained pain-free response with placebo was 10% (39/382; range 6% to 14%).
- The relative benefit of treatment compared with placebo was 3.2 (2.3 to 4.5; Analysis 12.5); the NNT was 4.5 (3.6 to 5.9).

Treating early, while headache was still in the mild pain phase was significantly more effective than treating established moderate or severe headache pain (z = 2.261; P = 0.024; see Summary of results B).

Sumatriptan 100 mg versus almotriptan 12.5 mg

Two studies (754 participants) in participants with moderate or severe baseline pain intensity provided data (Dodick 2002; Dowson 2002).

- The proportion of participants with a 24-hour sustained pain-free response with sumatriptan 100 mg was 29% (111/387; range 28% to 29%).
- The proportion of participants with a 24-hour sustained pain-free response with almotriptan 12.5 mg was 30% (110/367; range 25% to 35%).
- The relative benefit of sumatriptan compared with almotriptan was 0.96 (0.77 to 1.2; Analysis 16.2); there was no significant difference between treatments.

Sustained headache relief during the 24 hours postdose

All participants experiencing outcomes of headache relief must, by definition, have had moderate to severe pain at baseline.

Sumatriptan 50 mg versus placebo

Four studies (2526 participants) provided data (Sandrini 2002; Sheftell 2005 Study 1 and Study 2; Smith 2005).

- The proportion of participants with 24-hour sustained headache relief with sumatriptan 50 mg was 35% (454/1309; range 29% to 36%).
- The proportion of participants with 24-hour sustained headache relief with placebo was 18% (220/1217; range 17% to 21%).
- The relative benefit of treatment compared with placebo was 1.9 (1.7 to 2.2; Analysis 4.6); the NNT was 6.0 (5.0 to 7.6).

Sumatriptan 100 mg versus placebo

Six studies (4116 participants) provided data (Geraud 2000; Kaniecki 2006; Mathew 2003; Sandrini 2002; Sheftell 2005 Study 1 and Study 2).

- The proportion of participants with 24-hour sustained headache relief with sumatriptan 100 mg was 36% (922/2538; range 33% to 39%).
- The proportion of participants with 24-hour sustained headache relief with placebo was 17% (270/1578; range 14% to 25%).
- The relative benefit of treatment compared with placebo was 2.1 (1.9 to 2.4; Analysis 12.6); the NNT was 5.2 (4.6 to 6.0).

Sumatriptan 100 mg versus eletriptan 40 mg

Two studies (1998 participants) provided data (Mathew 2003; Sandrini 2002).

- The proportion of participants with 24-hour sustained headache relief with sumatriptan 100 mg was 34% (340/1001; range 33% to 38%).
- The proportion of participants with 24-hour sustained headache relief with eletriptan 40 mg was 43% (430/997; range 42% to 50%).
- The relative benefit of sumatriptan compared with eletriptan was 0.79 (0.70 to 0.88; Analysis 13.5); the NNT was 11 (7.5 to 20) in favour of eletriptan.

Summary of results A: Pain-free and headache relief

	Studies	Attacks treated	Treatment (%)	Placebo or comparator	Relative risk (95% CI)	NNT (95% CI)

				(%)		
Pain-free at 2 hours						
Sumatriptan 25 mg versus placebo (moderate or severe baseline pain intensity)	3	1108	25	9	2.7 (1.8 to 4.0)	6.2 (4.9 to 8.5)
Sumatriptan 50 mg versus placebo (moderate or severe baseline pain intensity)	13	6447	28	11	2.7 (2.4 to 3.1)	6.1 (5.5 to 6.9)
Sumatriptan 50 mg versus placebo (mild baseline pain intensity)	7	1514	46	23	2.0 (1.7 to 2.4)	4.4 (3.7 to 5.6)
Sumatriptan 100 mg versus placebo (moderate or severe baseline pain intensity)	16	6571	32	11	3.2 (2.8 to 3.6)	4.7 (4.3 to 5.1)
Sumatriptan 100 mg versus placebo (mild baseline pain intensity)	5	1240	58	24	2.4 (2.1 to 2.8)	3.0 (2.6 to 3.5)
Sumatriptan 25 mg versus rizatriptan 5 mg (moderate or severe baseline pain intensity)	2	2210	28	33	0.84 (0.74 to 0.95)	-18 (-11 to -62)
Sumatriptan 25 mg versus rizatriptan 10 mg (moderate or severe baseline pain intensity)	2	2231	28	39	0.70 (0.62 to 0.79)	-8.5 (-6.4 to -13)
Sumatriptan 50 mg versus effervescent ASA 1000 mg (moderate or severe baseline pain intensity)	2	726	32	26	1.2 (0.97 to 1.5)	Not calculated
Sumatriptan 50 mg versus rizatriptan 5 mg (moderate or severe baseline pain intensity)	2	2209	35	33	1.1 (0.95 to 1.2)	Not calculated
Sumatriptan 50 mg versus rizatriptan 10 mg (moderate or severe baseline pain intensity)	2	2230	35	39	0.89 (0.80 to 0.99)	-24 (-12 to -560)
Sumatriptan 50 mg versus eletriptan 40 mg (moderate or severe baseline pain intensity)	2	721	18	24	0.74 (0.55 to 0.98)	-16 (-8.2 to -270)
Sumatriptan 50 mg versus eletriptan 80 mg (moderate or severe baseline pain intensity)	2	706	18	30	0.58 (0.44 to 0.76)	-8.0 (-5.3 to -16)
Sumatriptan 100 mg versus eletriptan 40 mg (moderate or severe baseline pain intensity)	3	2263	24	32	0.74 (0.65 to 0.85)	-12 (-8.3 to -22)
Sumatriptan 100 mg versus eletriptan 80 mg (moderate or severe baseline pain intensity)	2	604	18	34	0.54 (0.41 to 0.72)	-6.5 (-4.5 to -12)

Sumatriptan 100 mg versus rizatriptan 10 mg (moderate or severe baseline pain intensity)	2	936	31	37	0.82 (0.69 to 0.98)	-16 (-8.1 to -410)
Sumatriptan 100 mg versus almotriptan 12.5 mg (moderate or severe baseline pain intensity)	2	754	33	28	1.2 (0.97 to 1.5)	Not calculated
Sumatriptan 100 mg versus ASA 900 mg + MCP 10 mg (moderate or severe baseline pain intensity)	2	575	26	16	1.6 (1.2 to 2.3)	10 (6.1 to 31)
Pain-free at 1 hour						
Sumatriptan 50 mg versus placebo (moderate or severe baseline pain intensity)	5	1735	5	2	2.6 (1.5 to 4.7)	33 (21 to 73)
Sumatriptan 50 mg versus placebo (mild baseline pain intensity)	5	1246	26	14	1.9 (1.5 to 2.4)	8.5 (6.2 to 13)
Sumatriptan 100 mg versus placebo (moderate or severe baseline pain intensity)	6	3176	7	2	4.0 (2.3 to 6.8)	18 (15 to 24)
Sumatriptan 100 mg versus placebo (mild baseline pain intensity)	5	1240	31	14	2.2 (1.8 to 2.8)	6.0 (4.7 to 8.3)
Sumatriptan 50 mg versus effervescent ASA 1000 mg (moderate or severe baseline pain intensity)	2	726	5	5	0.97 (0.53 to 1.8)	Not calculated
Sumatriptan 100 mg versus eletriptan 40 mg (moderate or severe baseline pain intensity)	3	2263	5	7	0.79 (0.57 to 1.1)	Not calculated
Sumatriptan 100 mg versus eletriptan 80 mg (moderate or severe baseline pain intensity)	2	604	6	13	0.48 (0.29 to 0.82)	-15 (-8.7 to -48)
Headache relief at 1 hour						
Sumatriptan 25 mg versus placebo	3	745	27	16	1.6 (1.2 to 2.3)	9.0 (5.8 to 20)
Sumatriptan 50 mg versus placebo	9	2766	27	14	1.8 (1.5 to 2.1)	7.5 (6.2 to 9.7)
Sumatriptan 100 mg versus placebo	10	3983	29	15	1.9 (1.6 to 2.2)	6.8 (5.8 to 8.3)
Sumatriptan 25 mg versus rizatriptan 5 mg	2	2210	34	37	0.91 (0.81 to 1.0)	Not calculated
Sumatriptan 25 mg versus rizatriptan 10 mg	2	2231	34	41	0.82 (0.74 to 0.91)	-14 (-8.8 to -30)

Sumatriptan 50 mg versus effervescent ASA 1000 mg	2	726	24	31	0.78 (0.61 to 0.98)	-15 (-7.5 to -270)
Sumatriptan 50 mg versus zolmitriptan 2.5 mg	2	1609	41	40	1.0 (0.90 to 1.1)	Not calculated
Sumatriptan 50 mg versus zolmitriptan 5 mg	2	1633	41	39	1.0 (0.92 to 1.2)	Not calculated
Sumatriptan 50 mg versus rizatriptan 5 mg	2	2209	37	37	0.99 (0.89 to 1.1)	Not calculated
Sumatriptan 50 mg versus rizatriptan 10 mg	2	2230	37	41	0.90 (0.81 to 1.0)	-23 (-12 to -410)
Sumatriptan 50 mg versus eletriptan 40 mg	2	721	25	25	0.99 (0.77 to 1.3)	Not calculated
Sumatriptan 50 mg versus eletriptan 80 mg	2	706	25	35	0.72 (0.57 to 0.91)	-10 (-6.1 to -33)
Sumatriptan 100 mg versus eletriptan 40 mg	3	2263	25	32	0.77 (0.67 to 0.88)	-13 (-8.9 to -26)
Sumatriptan 100 mg versus eletriptan 80 mg	2	604	23	35	0.65 (0.50 to 0.84)	-8.3 (-5.2 to -21)
Sumatriptan 100 mg versus rizatriptan 10 mg	2	936	26	34	0.76 (0.62 to 0.92)	-12 (-7.1 to -43)
Headache relief at 2 hours						
Sumatriptan 25 mg versus placebo	5	1580	56	32	1.7 (1.4 to 1.9)	4.2 (3.5 to 5.4)
Sumatriptan 50 mg versus placebo	19	8102	57	32	1.8 (1.7 to 1.9)	4.0 (3.7 to 4.4)
Sumatriptan 100 mg versus placebo	21	7811	61	32	1.9 (1.8 to 2.0)	3.5 (3.2 to 3.7)
Sumatriptan 200 mg versus placebo	3	749	72	26	2.8 (2.3 to 3.5)	2.1 (1.9 to 2.5)
Sumatriptan 300 mg versus placebo	2	709	67	25	2.7 (2.2 to 3.4)	2.4 (2.0 to 2.8)
Sumatriptan 25 mg versus rizatriptan 5 mg	2	2210	60	67	0.90 (0.84 to 0.95)	-14 (-9.1 to -34)
Sumatriptan 25 mg versus rizatriptan 10 mg	2	2231	60	70	0.86 (0.80 to 0.91)	-9.9 (-7.1 to -16)
Sumatriptan 50 mg versus effervescent ASA 1000 mg	2	726	53	42	1.3 (1.1 to 1.5)	8.7 (5.3 to 23)
Sumatriptan 50 mg versus zolmitriptan 2.5 mg	2	1609	67	66	1.0 (0.95 to 1.1)	Not calculated

Sumatriptan 50 mg versus zolmitriptan 5 mg	2	1633	67	66	1.0 (0.95 to 1.1)	Not calculated
Sumatriptan 50 mg versus rizatriptan 5 mg	3	2911	65	66	0.98 (0.93 to 1.0)	Not calculated
Sumatriptan 50 mg versus rizatriptan 10 mg	2	2227	64	70	0.91 (0.86 to 0.97)	-16 (-9.9 to -43)
Sumatriptan 50 mg versus eletriptan 40 mg	2	721	51	60	0.85 (0.75 to 0.97)	-11 (-6.1 to -54)
Sumatriptan 50 mg versus eletriptan 80 mg	2	706	51	66	0.78 (0.69 to 0.89)	-7.0 (-4.7 to -14)
Sumatriptan 100 mg versus eletriptan 40 mg	3	2263	55	62	0.88 (0.82 to 0.95)	-14 (-8.8 to -31)
Sumatriptan 100 mg versus eletriptan 80 mg	2	604	51	65	0.78 (0.68 to 0.89)	-6.9 (-4.5 to -15)
Sumatriptan 100 mg versus paracetamol 1000 mg + MCP 10 mg	2	1035	45	43	1.1 (0.92 to 1.2)	Not calculated
Sumatriptan 100 mg versus ASA 900 mg + MCP 10 mg	2	575	50	46	1.1 (0.92 to 1.3)	Not calculated
Sustained pain-free during the 24 hours postdose						
Sumatriptan 50 mg versus placebo (moderate or severe baseline pain intensity)	4	2526	17	7	2.6 (2.1 to 3.4)	9.5 (7.7 to 12)
Sumatriptan 50 mg versus placebo (mild baseline pain intensity)	4	866	28	10	2.8 (2.1 to 3.9)	5.5 (4.3 to 7.6)
Sumatriptan 100 mg versus placebo (moderate or severe baseline pain intensity)	6	2891	24	8	2.8 (2.4 to 3.5)	6.5 (5.6 to 7.8)
Sumatriptan 100 mg versus placebo (mild baseline pain intensity)	3	771	33	10	3.2 (2.3 to 4.5)	4.5 (3.6 to 5.9)
Sumatriptan 100 mg versus almotriptan 12.5 mg (moderate or severe baseline pain intensity)	2	754	29	30	0.96 (0.77 to 1.2)	Not calculated
Sustained headache relief during the 24 hours postdose						
Sumatriptan 50 mg versus placebo	4	2526	35	18	1.9 (1.7 to 2.2)	6.0 (5.0 to 7.6)
Sumatriptan 100 mg versus placebo	6	4116	36	17	2.1 (1.9 to 2.4)	5.2 (4.6 to 6.0)

Sumatriptan 100 mg versus eletriptan 40 mg	2	1998	34	43	0.79 (0.70 to 0.88)	-11 (-7.5 to -20)

Summary of results B: Statistical tests for the effect of dose and baseline pain intensity

	z	P
Pain-free at 2 hours		
Sumatriptan 50 mg, mild versus moderate/severe baseline pain	2.450	0.014
Sumatriptan 50 mg versus 100 mg (moderate/severe baseline pain)	3.798	0.0001
Sumatriptan 50 mg versus 100 mg (mild baseline pain)	3.124	0.002
Sumatriptan 100 mg, mild versus moderate/severe baseline pain	4.351	< 0.00006
Headache relief at 2 hours		
Sumatriptan 50 mg versus 100 mg	2.585	0.010
Sumatriptan 100 mg versus 200 mg	5.212	< 0.00006
Sustained pain-free during the 24 hours postdose		
Sumatriptan 50 mg, mild versus moderate/severe baseline pain	2.648	0.008
Sumatriptan 50 mg versus 100 mg (moderate/severe baseline pain)	2.663	0.008
Sumatriptan 100 mg, mild versus moderate/severe baseline pain	2.261	0.024

Subgroup analyses

Formulation: dispersible/rapid-release tablet versus standard tablet

For headache relief at two hours (Analysis 12.14) with sumatriptan 100 mg versus placebo, there was no difference between dispersible (i.e. disintegrating)/rapid-release formulations and standard tablets (P = 0.59). There were insufficient data to investigate effect of formulation for other doses or outcomes.

Sensitivity analyses

We carried out sensitivity analyses to take into consideration and assess the effect of variation in methodological quality of the included studies. We considered studies with an Oxford Quality Score of 2 of 5 to be at greater risk of bias and therefore analysed them separately for each outcome. Where there were insufficient data to provide a meaningful comparison of these lower-quality trials with the higher quality trials (scoring 3 or more of 5) for a particular outcome, we performed sensitivity analyses simply to remove the lower-quality trials from the original all-trials analyses.

There were insufficient data to carry out any sensitivity analyses for participants with and without aura.

Pain-free at two hours

Sumatriptan 50 mg versus placebo

Of the 12 studies originally analysed comparing sumatriptan 50 mg with placebo in participants with moderate or severe baseline pain intensity, two had a quality score of 2 of 5 (Cutler 1995; Savani 1999). There was no significant difference (P = 0.30) between the two groups of studies (Analysis 4.14).

Of the six studies originally analysed comparing sumatriptan 50 mg with placebo in participants with mild baseline pain intensity, two had a quality score of 2 of 5 (Carpay 2004; Pini 1999). There was no significant difference between the two groups of studies (analysis not shown).

Sumatriptan 100 mg versus placebo

Of the 16 studies originally analysed comparing sumatriptan 100 mg with placebo in participants with moderate or severe baseline pain intensity, three had a quality score of 2 of 5 (Cutler 1995; Dodick 2002; Ensink 1991). There was no significant difference (P = 0.32) between the two groups of studies (Analysis 12.15).

Of the four studies originally analysed comparing sumatriptan 100 mg with placebo in participants with mild baseline pain intensity, one had a quality score of 2 of 5 (Carpay 2004). Removing this study from the analysis made no significant difference to the calculated relative benefit of treatment versus placebo (analysis not shown).

Pain-free at one hour

None of the 10 studies providing data on pain-free at one hour in participants with moderate or severe baseline pain intensity had a quality score of less than 3 of 5.

Of the four studies originally analysed comparing sumatriptan (either 50 mg or 100 mg) with placebo in participants with mild baseline pain intensity, one had a quality score of 2 of 5 (Carpay 2004). Removing this study from the analysis of either dose made no significant difference to the calculated relative benefit of treatment versus placebo (analysis not shown).

Headache relief at one hour

Sumatriptan 50 mg versus placebo

Of the nine studies originally analysed comparing sumatriptan 50 mg with placebo, only one had a quality score of 2 of 5 (Savani 1999). Removing this study from the analysis made no significant difference to the calculated relative benefit of treatment versus placebo (Analysis 4.15).

Headache relief at two hours

Sumatriptan 25 mg versus placebo

Of the five studies originally analysed comparing sumatriptan 50 mg with placebo, only one had a quality score of 2 of 5 (Cutler 1995). Removing this study from the analysis made no significant difference to the calculated relative benefit of treatment versus placebo (Analysis 1.10).

Sumatriptan 50 mg versus placebo

Of the 18 studies originally analysed comparing sumatriptan 50 mg with placebo, four had a quality score of 2 of 5 (Bussone 2000; Cutler 1995; Lines 2001; Savani 1999). There was a significant difference between the studies with a quality score of 2 and those with a score of 3 or more (z = 2.61, P = 0.009) (Analysis 4.16). Removing low-quality studies did not substantially change the calculated relative benefit and NNT.

Sumatriptan 100 mg versus placebo

Of the 20 studies originally analysed comparing sumatriptan 50 mg with placebo, four had a quality score of 2 of 5 (Cutler 1995; Dahlof 1991; Ensink 1991; Patten 1991). There was a significant difference between the studies with a quality score of 2 and those with a score of 3 or more (z = 2.98, P = 0.003) (Analysis 12.16). Removing low-quality studies did not substantially change the calculated relative benefit and NNT.

Sustained pain-free during the 24 hours postdose

None of the studies providing data for 24-hour sustained freedom from pain in participants with moderate or severe baseline pain scored a quality score of less than 3, so no sensitivity analyses were possible.

Of the four and three studies originally analysed for this outcome comparing sumatriptan 50 mg and 100 mg, respectively, with placebo in participants with mild baseline pain, one study had a quality score of 2 of 5 (Carpay 2004). Removing this study from the analysis of either dose made no significant difference to the calculated relative benefit of treatment versus placebo (analysis not shown).

Use of rescue medication

All studies but one (Schulman 2003) allowed participants whose symptoms were not adequately controlled to take additional rescue or 'escape' medication (usually a different analgesic, or in some studies a second dose of test medication). Participants were asked to wait, usually for two hours, before taking any additional medication in order to give the test medication enough time to have an effect. Use of rescue medication at or after a defined time point was reported in most studies and is a measure of treatment failure (lack of efficacy). The time over which use of rescue medication was measured varied between studies. Some reported use of rescue medication up to four hours after initial dosing, while the others reported use of rescue medication up to 24 hours after initial dosing.

Sumatriptan 25 mg versus placebo

None of the included studies provided data for this comparison up to 24 hours after initial dosing.

Two studies (1282 participants) provided data for the use of rescue medication up to four hours after initial dosing, in participants with moderate or severe baseline pain intensity (Goldstein 1998; Kolodny 2004).

- The proportion of participants requiring rescue medication with sumatriptan 25 mg was 24% (207/853; range 23% to 25%).
- The proportion of participants requiring rescue medication with placebo was 41% (175/429; range 39% to 45%).
- The relative benefit of treatment compared with placebo was 0.57 (0.48 to 0.68; Analysis 1.4); the NNTp was 6.1 (4.6 to 9.0).

Sumatriptan 50 mg verus placebo

Four studies (2079 participants) provided data for the use of rescue medication up to 24 hours after initial dosing, in participants with moderate or severe baseline pain intensity (Diener 2004a; Ishkanian 2007; Lipton 2000; Smith 2005).

- The proportion of participants requiring rescue medication with sumatriptan 50 mg was 20% (266/1339; range 7% to 51%).
- The proportion of participants requiring rescue medication with placebo was 42% (309/740; range 8% to 63%).
- The relative benefit of treatment compared with placebo was 0.77 (0.68 to 0.87; Analysis 4.7); the NNTp was 4.6 (3.8 to 5.6).

Two studies (384 participants) provided data for the use of rescue medication up to 24 hours after initial dosing, in participants with mild baseline pain intensity (Jelinski 2006; Pini 1999).

- The proportion of participants requiring rescue medication with sumatriptan 50 mg was 30% (66/221; range 23% to 35%).
- The proportion of participants requiring rescue medication with placebo was 58% (94/163; range 48% to 62%).
- The relative benefit of treatment compared with placebo was 0.54 (0.42 to 0.68; Analysis 4.7); the NNTp was 3.6 (2.7 to 5.5).

Treating early, while headache was still in the mild pain phase did not significantly affect the use of rescue medication.

Five studies (2098 participants) provided data for the use of rescue medication up to four hours after initial dosing, in participants with moderate or severe baseline pain intensity (Dahlof 2009; Diener 2004b; Goldstein 1998; Goldstein 2005; Kolodny 2004).

- The proportion of participants requiring rescue medication with sumatriptan 50 mg was 23% (296/1278; range 12% to 41%).
- The proportion of participants requiring rescue medication with placebo was 45% (366/820; range 14% to 66%).
- The relative benefit of treatment compared with placebo was 0.56 (0.49 to 0.63; Analysis 4.7); the NNTp was 4.7 (3.9 to 5.8).

Sumatriptan 100 mg versus placebo

Six studies (2810 participants) provided data for the use of rescue medication up to 24 hours after initial dosing, in participants with moderate or severe baseline pain intensity (Dodick 2002; Geraud 2000; Goadsby 2000; Havanka 2000; Mathew 2003; Tfelt-Hansen 1995).

- The proportion of participants requiring rescue medication with sumatriptan 100 mg was 33% (621/1877; range 26% to 63%).
- The proportion of participants requiring rescue medication with placebo was 58% (543/933; range 53% to 81%).
- The relative benefit of treatment compared with placebo was 0.57 (0.52 to 0.62; Analysis 12.7); the NNTp was 4.0 (3.5 to 4.7).

Three studies (1027 participants) provided data for the use of rescue medication up to four hours after initial dosing, in participants with moderate or severe baseline pain intensity (Dowson 2002; Goadsby 1991; Tfelt-Hansen 1998).

- The proportion of participants requiring rescue medication with sumatriptan 100 mg was 27% (179/675; range 20% to 41%).
- The proportion of participants requiring rescue medication with placebo was 54% (189/352; range 32% to 88%).
- The relative benefit of treatment compared with placebo was 0.55 (0.47 to 0.65; Analysis 12.7); the NNTp was 3.7 (3.0 to 4.8).

Sumatriptan 25 mg versus rizatriptan 5 mg

Two studies (1698 participants) provided data for the use of rescue medication up to four hours after initial dosing, in participants with moderate or severe baseline pain intensity (Goldstein 1998; Kolodny 2004).

- The proportion of participants requiring rescue medication with sumatriptan 25 mg was 24% (207/853; range 23% to 25%).
- The proportion of participants requiring rescue medication with rizatriptan 5 mg was 25% (213/845; range 23% to 30%).
- The relative benefit of sumatriptan compared with rizatriptan was 0.96 (0.82 to 1.1; Analysis 2.4); there was no significant difference between treatments.

Sumatriptan 25 mg versus rizatriptan 10 mg

Two studies (1716 participants) provided data for the use of rescue medication up to four hours after initial dosing, in participants with moderate or severe baseline pain intensity (Goldstein 1998; Kolodny 2004).

- The proportion of participants requiring rescue medication with sumatriptan 25 mg was 24% (207/853; range 23% to 25%).
- The proportion of participants requiring rescue medication with rizatriptan 10 mg was 20% (175/863; range 19% to 23%).
- The relative benefit of sumatriptan compared with rizatriptan was 1.2 (1.0 to 1.4; Analysis 3.4); there was no significant difference between treatments.

Sumatriptan 50 mg versus rizatriptan 5 mg

Two studies (1696 participants) provided data for the use of rescue medication up to four hours after initial dosing, in participants with moderate or severe baseline pain intensity (Goldstein 1998; Kolodny 2004).

- The proportion of participants requiring rescue medication with sumatriptan 50 mg was 20% (167/851; range 19% to 21%).
- The proportion of participants requiring rescue medication with rizatriptan 5 mg was 25% (213/845; range 23% to 30%).
- The relative benefit of sumatriptan compared with rizatriptan was 0.78 (0.65 to 0.93; Analysis 8.4); the NNTp was 18 (10 to 62).

Sumatriptan 50 mg versus rizatriptan 10 mg

Two studies (1714 participants) provided data for the use of rescue medication up to four hours after initial dosing, in participants with moderate or severe baseline pain intensity (Goldstein 1998; Kolodny 2004).

- The proportion of participants requiring rescue medication with sumatriptan 50 mg was 20% (167/851; range 19% to 21%).
- The proportion of participants requiring rescue medication with rizatriptan 10 mg was 20% (175/863; range 19% to 23%).
- The relative benefit of sumatriptan compared with rizatriptan was 0.97 (0.80 to 1.2; Analysis 9.4); there was no significant difference between treatments.

Sumatriptan 100 mg versus eletriptan 40 mg

Two studies (1918 participants) provided data for the use of rescue medication up to 24 hours after initial dosing, in participants with moderate or severe baseline pain intensity (Goadsby 2000; Mathew 2003).

- The proportion of participants requiring rescue medication with sumatriptan 100 mg was 27% (261/960; range 27% to 29%).
- The proportion of participants requiring rescue medication with eletriptan 40 mg was 21% (203/958; range 20% to 29%).
- The relative benefit of sumatriptan compared with rizatriptan was 1.3 (1.1 to 1.5; Analysis 13.6); the NNTp was 17 (10 to 46) in favour of eletriptan.

Sumatriptan 100 mg versus paracetamol 1000 mg + metoclopramide 10 mg

Two studies (1243 participants) provided data for the use of rescue medication up to 24 hours after initial dosing, in participants with moderate or severe baseline pain intensity (GL/MIG/001/92; GL/MIG/001A/92).

- The proportion of participants requiring rescue medication with sumatriptan 100 mg was 33% (198/606; range 27% to 37%).

- The proportion of participants requiring rescue medication with paracetamol 1000 mg + MCP 10 mg was 38% (245/637; range 32% to 44%).
- The relative benefit of sumatriptan compared with paracetamol + MCP was 0.86 (0.74 to 0.99; Analysis 17.3); the NNTp was 17 (9.0 to 210).

Summary of results C: Use of rescue medication

	Studies	Attacks treated	Treatment (%)	Placebo or comparator (%)	Relative risk (95% CI)	NNTp (95% CI)
Use of rescue medication up to 24 hours after initial dosing						
Sumatriptan 50 mg versus placebo (moderate or severe baseline pain intensity)	4	2079	20	42	0.77 (0.68 to 0.87)	4.6 (3.8 to 5.6)
Sumatriptan 50 mg versus placebo (mild baseline pain intensity)	2	384	30	58	0.54 (0.42 to 0.68)	3.6 (2.7 to 5.5)
Sumatriptan 100 mg versus placebo	6	2810	33	58	0.57 (0.52 to 0.62)	4.0 (3.5 to 4.7)
Sumatriptan 100 mg versus eletriptan 40 mg	2	1918	27	21	1.3 (1.1 to 1.5)	-17 (-10 to -46)
Sumatriptan 100 mg versus paracetamol 1000 mg + metoclopramide 10 mg	2	1243	33	38	0.86 (0.74 to 0.99)	17 (9.0 to 210)
Use of rescue medication up to 4 hours after initial dosing						
Sumatriptan 25 mg versus placebo	2	1282	24	41	0.57 (0.48 to 0.68)	6.1 (4.6 to 9.0)
Sumatriptan 50 mg versus placebo	5	2098	23	45	0.56 (0.50 to 0.64)	4.7 (3.9 to 5.8)
Sumatriptan 100 mg versus placebo	3	1027	27	54	0.55 (0.47 to 0.65)	3.7 (3.0 to 4.8)
Sumatriptan 25 mg versus rizatriptan 5 mg	2	1698	24	25	0.96 (0.82 to 1.1)	Not calculated
Sumatriptan 25 mg versus rizatriptan 10 mg	2	1716	24	20	1.2 (1.0 to 1.4)	Not calculated
Sumatriptan 50 mg versus rizatriptan 5 mg	2	1696	20	25	0.78 (0.65 to 0.93)	18 (10 to 62)
Sumatriptan 50 mg versus rizatriptan 10 mg	2	1714	20	20	0.97 (0.80 to 1.2)	Not calculated

Relief of headache-associated symptoms

In general, relief of headache-associated symptoms (defined as a symptom reduction from any intensity at baseline to none at two hours) was inconsistently reported. Of the 28 studies that reported any data for symptom relief, only seven reported on relief of all four major symptoms of interest. Not all studies reported baseline incidence of associated symptoms from which relief could be calculated, however the majority reported presence of symptoms two hours after treatment. The incidence of vomiting was very low in all studies and where reported did not permit analysis.

Fourteen of the studies providing data on relief of associated symptoms included a small number (< 10%) of participants with mild baseline pain intensity. It is possible that these participants had fewer or less severe associated symptoms, but the number was considered small enough that even if this were so, there would not be a major effect on the overall result; these studies were therefore included in any pooled analyses to which they were relevant.

Effects of treatment on relieving headache-associated symptoms are presented in Summary of results D. Sumatriptan at doses of 25 mg, 50 mg, and 100 mg showed efficacy in relief of the associated symptoms of nausea, photophobia, and phonophobia, compared to placebo. There was no obvious dose response relationship over 25 mg to 100 mg. The majority of the data were for participants with moderate or severe baseline pain intensity, for whom about 45% to 50% of symptoms present at baseline were relieved within two hours of sumatriptan treatment, while about 30% to 35% were relieved with placebo (Analysis 1.5; Analysis 4.8; Analysis 12.8), giving NNTs of 4 to 8.

Three studies in participants with mild baseline pain intensity provided data on relief of headache-associated symptoms. About 50% to 60% of symptoms present at baseline were relieved within two hours of sumatriptan treatment, while only 10% to 20% were relieved with placebo (Analysis 4.9; Analysis 12.9), giving NNTs 2 to 3. These results must be interpreted cautiously due to the fact that only small numbers of participants were involved in the same three studies providing data for relief of each associated symptom. In addition the studies made no comment on the severity of the symptoms, and it may be that the symptoms present at baseline in participants with moderate or severe headache are not comparable with those present at baseline in participants with mild headache.

Sumatriptan 50 mg was inferior to eletriptan 40 mg for the relief of nausea (NNT of 8.2 in favour of eletriptan), but no significant difference was found between the two for relief of photophobia or phonophobia (Analysis 10.4). Eletriptan 80 mg, on the other hand, was found to be superior to sumatriptan 50 mg for the relief of photophobia and phonophobia (NNTs of 6.1 and 9.0 respectively), but there was no significant difference between the two for relief of nausea (Analysis 11.4).

Sumatriptan 100 mg was inferior to eletriptan 40 mg for the relief of nausea, photophobia, and phonophobia, with NNTs of 11 to 16 in favour of eletriptan (Analysis 13.7). Similarly sumatriptan 100 mg was inferior to eletriptan 80 mg for the relief of nausea and photophobia, with NNTs of 8.9 and 6.4, respectively, in favour of eletriptan (Analysis 14.5). There was no clear difference between sumatriptan 100 mg and ASA 900 mg + MCP 10 mg for the relief of nausea (Analysis 18.3), or paracetamol 1000 mg + MCP 10 mg for the relief of either photophobia or phonophobia (Analysis 17.2).

Summary of results D: relief of associated symptoms at 2 hours

Intervention	Studies	Attacks with symptom present	Treatment (%)	Placebo or comparator (%)	Relative risk (95% CI)	NNT
Nausea						
Sumatriptan 25 mg versus placebo	4	550	48	34	1.5 (1.2 to 1.9)	7.2 (4.5 to 18)
Sumatriptan 50 mg versus placebo (moderate or severe baseline pain intensity)	7	973	45	33	1.4 (1.2 to 1.7)	8.1 (5.4 to 16)
Sumatriptan 50 mg versus placebo (mild baseline pain intensity)	3	280	54	7	6.9 (3.8 to 13)	2.2 (1.8 to 2.7)
Sumatriptan 100 mg versus placebo (moderate or severe baseline pain intensity)	14	2996	45	30	1.5 (1.3 to 1.7)	6.9 (5.5 to 9.1)
Sumatriptan 100 mg versus placebo (mild baseline pain intensity)	3	265	45	7	5.9 (3.2 to 11)	2.7 (2.1 to 3.6)

Sumatriptan 50 mg versus eletriptan 40 mg	2	374	38	50	0.76 (0.60 to 0.95)	-8.2 (-4.5 to 44)
Sumatriptan 50 mg versus eletriptan 80 mg	2	370	38	45	0.85 (0.67 to 1.1)	Not calculated
Sumatriptan 100 mg versus eletriptan 40 mg	3	1478	49	55	0.87 (0.79 to 0.96)	-16 (-8.7 to -77)
Sumatriptan 100 mg versus eletriptan 80 mg	2	408	49	60	0.83 (0.69 to 0.99)	-8.9 (-4.8 to -60)
Sumatriptan 100 mg versus ASA 900 mg + MCP 10 mg	2	410	31	35	0.91 (0.69 to 1.2)	Not calculated
Photophobia						
Sumatriptan 25 mg versus placebo	3	411	40	20	1.8 (1.3 to 2.5)	5.0 (3.5 to 8.9)
Sumatriptan 50 mg versus placebo (moderate or severe baseline pain intensity)	6	1144	45	32	1.4 (1.2 to 1.7)	7.8 (5.4 to 14)
Sumatriptan 50 mg versus placebo (mild baseline pain intensity)	3	483	53	18	3.0 (2.2 to 4.0)	2.9 (2.3 to 3.7)
Sumatriptan 100 mg versus placebo (moderate or severe baseline pain intensity)	9	2494	49	25	1.9 (1.6 to 2.1)	4.2 (3.7 to 5.1)
Sumatriptan 100 mg versus placebo (mild baseline pain intensity)	3	475	57	18	3.2 (2.4 to 4.3)	2.5 (2.1 to 3.2)
Sumatriptan 50 mg versus eletriptan 40 mg	2	528	41	49	0.83 (0.69 to 1.0)	Not calculated
Sumatriptan 50 mg versus eletriptan 80 mg	2	508	41	57	0.72 (0.60 to 0.86)	-6.1 (-4.0 to -13)
Sumatriptan 100 mg versus eletriptan 40 mg	3	1692	51	60	0.85 (0.78 to 0.93)	-12 (-7.6 to -26)
Sumatriptan 100 mg versus eletriptan 80 mg	2	457	47	63	0.76 (0.64 to 0.89)	-6.4 (-4.1 to -15)
Phonophobia						
Sumatriptan 50 mg versus placebo (moderate or severe baseline pain intensity)	4	852	50	37	1.4 (1.2 to 1.6)	7.8 (5.1 to 16)
Sumatriptan 50 mg versus placebo (mild baseline pain intensity)	3	413	52	18	3.0 (2.2 to 4.2)	2.9 (2.3 to 3.9)
Sumatriptan 100 mg versus placebo (moderate or severe baseline pain intensity)	7	2118	49	26	1.8 (1.6 to 2.1)	4.3 (3.7 to 5.3)

Sumatriptan 100 mg versus placebo (mild baseline pain intensity)	3	400	63	18	3.7 (2.7 to 5.1)	2.2 (1.8 to 2.7)
Sumatriptan 50 mg versus eletriptan 40 mg	2	517	47	53	0.87 (0.73 to 1.0)	Not calculated
Sumatriptan 50 mg versus eletriptan 80 mg	2	508	47	58	0.81 (0.69 to 0.96)	-9.0 (-5.1 to -41)
Sumatriptan 100 mg versus eletriptan 40 mg	2	1361	51	60	0.84 (0.76 to 0.92)	-11 (-6.8 to -24)
Photophobia or phonophobia						
Sumatriptan 50 mg versus placebo	2	440	55	31	2.1 (1.6 to 2.8)	4.2 (3.0 to 6.9)
Sumatriptan 100 mg versus placebo	5	1073	46	24	2.0 (1.7 to 2.5)	4.6 (3.6 to 6.2)
Sumatriptan 100 mg versus paracetamol 1000 mg + MCP 10 mg	2	1001	32	32	0.99 (0.83 to 1.2)	Not calculated

We also analysed studies according to the presence of associated symptoms two hours after treatment, irrespective of whether they were present at baseline, and calculated NNTps (Appendix 6). Significantly fewer participants reported symptoms of nausea, photophobia, or phonophobia with sumatriptan 25 mg, 50 mg, and 100 mg than with placebo, with no obvious dose response relationship. Again, the majority of the data were for participants treating established moderate or severe migraine attacks. Significantly fewer participants reported photophobia at two hours with sumatriptan than with any comparator, with NNTps ranging from 5.7 to 7.1. Similarly, fewer participants reported nausea and phonophobia with sumatriptan than with any comparator, although the difference was less pronounced, with NNTps ranging from 7.3 to 15. There was no significant difference between sumatriptan of any dose and placebo for incidence of vomiting at two hours. The small amount of data available for participants treating mild migraine attacks indicated that sumatriptan 50 mg and 100 mg were also effective against headache-associated symptoms at two hours compared to placebo. There was no obvious dose response relationship between the 50 mg and 100 mg doses. Calculated NNTps were not significantly different to those for participants treating moderate or severe headache, with the exception of phonophobia, for which sumatriptan 100 mg administered during the mild pain phase was significantly more effective (P = 0.002) than the same dose administered when the headache had reached moderate or severe intensity.

Significantly fewer participants reported nausea with rizatriptan 5 mg and 10 mg than with sumatriptan 25 mg or 50 mg (NNTps ranged from 15 to 23 in favour of rizatriptan). Rizatriptan 10 mg was also more effective against photophobia and phonophobia after two hours than sumatriptan 25 mg. Eletriptan 40 mg and 80 mg were significantly superior to sumatriptan 100 mg against nausea, photophobia, and phonophobia at two hours (NNTps ranged from 7 to 14 in favour of eletriptan). However, only eletriptan 80 mg was found to be significantly better than sumatriptan 50 mg against photophobia and phonophobia at two hours (NNTps of 8.0 and 14 in favour of eletriptan). Otherwise there were no significant differences in the presence of headache-associated symptoms at two hours between sumatriptan and the other active migraine treatments for which data were analysed.

Relief of functional disability

Few studies reported relief of functional disability (defined as improvement from moderate or severe disability at baseline to mild or none at two hours on a four-point scale). The following analyses involve studies in which participants had moderate or severe (or predominantly moderate or severe) baseline pain. Only one study (Carpay 2004) assessing participants with mild baseline pain intensity reported relief of functional disability as defined in this way, and therefore no separate pooled analyses could be performed.

Sumatriptan 25 mg versus placebo

Three studies (381 participants) provided data (160-104; Cutler 1995; Sargent 1995).

- The proportion of participants with relief of functional disability at two hours with sumatriptan 25 mg was 49% (107/220; range 33% to 52%).
- The proportion of participants with relief of functional disability at two hours with placebo was 32% (51/161; range 15% to 50%).
- The relative benefit of treatment compared with placebo was 1.4 (1.1 to 1.8; Analysis 1.6); the NNT was 5.9 (3.7 to 14).

Sumatriptan 50 mg versus placebo

Four studies (607 participants) provided data (160-104; Cutler 1995; Sandrini 2002; Sargent 1995).

- The proportion of participants with relief of functional disability at two hours with sumatriptan 50 mg was 49% (186/378; range 29% to 58%).
- The proportion of participants with relief of functional disability at two hours with placebo was 31% (72/229; range 15% to 50%).
- The relative benefit of treatment compared with placebo was 1.5 (1.2 to 1.8; Analysis 4.10); the NNT was 5.6 (3.9 to 10).

Sumatriptan 100 mg versus placebo

Six studies (1827 participants) provided data (Cutler 1995; Goadsby 2000; Havanka 2000; Mathew 2003; Sandrini 2002; Sargent 1995).

- The proportion of participants with relief of functional disability at two hours with sumatriptan 100 mg was 58% (651/1113; range 46% to 62%).
- The proportion of participants with relief of functional disability at two hours with placebo was 31% (220/714; range 15% to 34%).
- The relative benefit of treatment compared with placebo was 1.9 (1.7 to 2.1; Analysis 12.10); the NNT was 3.6 (3.1 to 4.3).

Sumatriptan 50 mg versus eletriptan 40 mg

Two studies (590 participants) provided data (160-104; Sandrini 2002).

- The proportion of participants with relief of functional disability at two hours with sumatriptan 50 mg was 51% (153/298; range 46% to 58%).
- The proportion of participants with relief of functional disability at two hours with eletriptan 40 mg was 62% (180/292; range 60% to 63%).
- The relative benefit of sumatriptan compared with eletriptan was 0.83 (0.72 to 0.96; Analysis 10.5); the NNT was 9.7 (5.5 to 43) in favour of eletriptan.

Sumatriptan 50 mg versus eletriptan 80 mg

Two studies (570 participants) provided data (160-104; Sandrini 2002).

- The proportion of participants with relief of functional disability at two hours with sumatriptan 50 mg was 51% (153.298; range 46% to 58%).
- The proportion of participants with relief of functional disability at two hours with eletriptan 80 mg was 62% (168/272; range 55% to 68%).
- The relative benefit of sumatriptan compared with eletriptan was 0.84 (0.73 to 0.97; Analysis 11.5); the NNT was 9.6 (5.4 to 43) in favour of eletriptan.

Sumatriptan 100 mg versus eletriptan 40 mg

Three studies (1880 participants) provided data (Goadsby 2000; Mathew 2003; Sandrini 2002).

- The proportion of participants with relief of functional disability at two hours with sumatriptan 100 mg was 59% (553/936; range 46% to 62%).
- The proportion of participants with relief of functional disability at two hours with eletriptan 40 mg was 68% (645/944; range 63% to 70%).
- The relative benefit of sumatriptan compared with eletriptan was 0.86 (0.81 to 0.92; Analysis 13.8); the NNT was 11 (7.4 to 20) in favour of eletriptan.

Sumatriptan 100 mg versus eletriptan 80 mg

Two studies (516 participants) provided data (Goadsby 2000; Sandrini 2002).

- The proportion of participants with relief of functional disability at two hours with sumatriptan 100 mg was 51% (129/255; range 46% to 56%).
- The proportion of participants with relief of functional disability at two hours with eletriptan 80 mg was 66% (173/261; range 55% to 78%).
- The relative benefit of sumatriptan compared with eletriptan was 0.77 (0.67 to 0.90; Analysis 14.6); the NNT was 6.4 (4.2 to 14) in favour of eletriptan.

We also analysed studies according to the presence of functional disability (of moderate or severe intensity on a four-point scale) two hours after treatment, and irrespective of whether it was present at baseline, and calculated NNTps (Appendix 6). Significantly fewer participants reported functional disability two hours after treatment with sumatriptan 25 mg, 50 mg, and 100 mg than with placebo, with the 100 mg dose having a lower (better) NNTp of 3.8 than the two lower doses (NNTps of 6.4 and 6.7, respectively). Eletriptan 40 mg and 80 mg were significantly more effective than sumatriptan 50 mg and 100 mg against functional disability at two hours (NNTps ranged from 6.6 to 13 in favour of eletriptan).

Adverse events

Details of results for adverse events and withdrawals in individual studies are provided in Appendix 7.

All except five studies (Dodick 2002; Lines 2001; Goadsby 1991; Goldstein 2005; Sandrini 2002) reported on the total number of participants experiencing any adverse event after treatment, although there was significant variability in many details of adverse event reporting in those studies providing data. Most studies appeared to collect data using spontaneous reports in diary cards and at follow-up review after the end of treatment. The duration over which data were collected was not always specific, and where it was, there were differences across studies. Most studies probably collected data during the 24 hours postdose, but some specified different time periods: Sargent 1995 specified 72 hours; Pini 1995 "during the study"; Dahlof 2009 six days; 160-104, Mathew 2003, and Sheftell 2005 seven days; and GL/MIG/001/92, GL/MIG/001A/92, GL/MIG/002, and GL/MIG/002A collected data over several weeks. The majority of studies reported adverse events regardless of their causal relationship to the study drug, but eight studies (Carpay 2004; Dahlof 1991; Freitag 2001; Jelinski 2006; Kaniecki 2006; Lipton 2000; Pini 1995; Sheftell 2005) reported only events considered to be related to the study medication.

In some studies a second, and sometimes third, dose of study medication was taken, and in all but one study rescue medication was allowed if there was an inadequate response after a given period of time. It is likely that in all cases adverse event data continued to be collected after such additional medication. Furthermore, a number of studies treated more than one attack. In Gallagher 2000, Goldstein 1998, and Kolodny 2004 first attack data were reported for adverse events, while Lipton 2000 reported

events in all attacks combined. Banerjee 1992, Bussone 2000, Dahlof 1991, Diener 2004b, DKSMSG 1999, Gruffyd-Jones 2001, Latere 1991, Myllyla 1998, Patten 1991, Pfaffenrath 1998, Sandrini 2007, Savani 1999, Schulman 2003, Tfelt-Hansen 1995, and Thomson 1992 reported events per participant, but it is unclear how multiple attacks were combined.

Despite these inconsistencies, we have included as much data as possible in the adverse event analyses in order to be more inclusive and conservative, but analyses of pooled data on adverse events should be interpreted cautiously.

Treatments were generally described as well tolerated, with most adverse events being of mild or moderate severity and self limiting.

Participants experiencing any adverse event during the 24 hours postdose

Sumatriptan 25 mg versus placebo

Four studies (1550 participants) in participants with moderate or severe baseline pain intensity provided data (Cutler 1995; Goldstein 1998; Kolodny 2004; Pfaffenrath 1998).

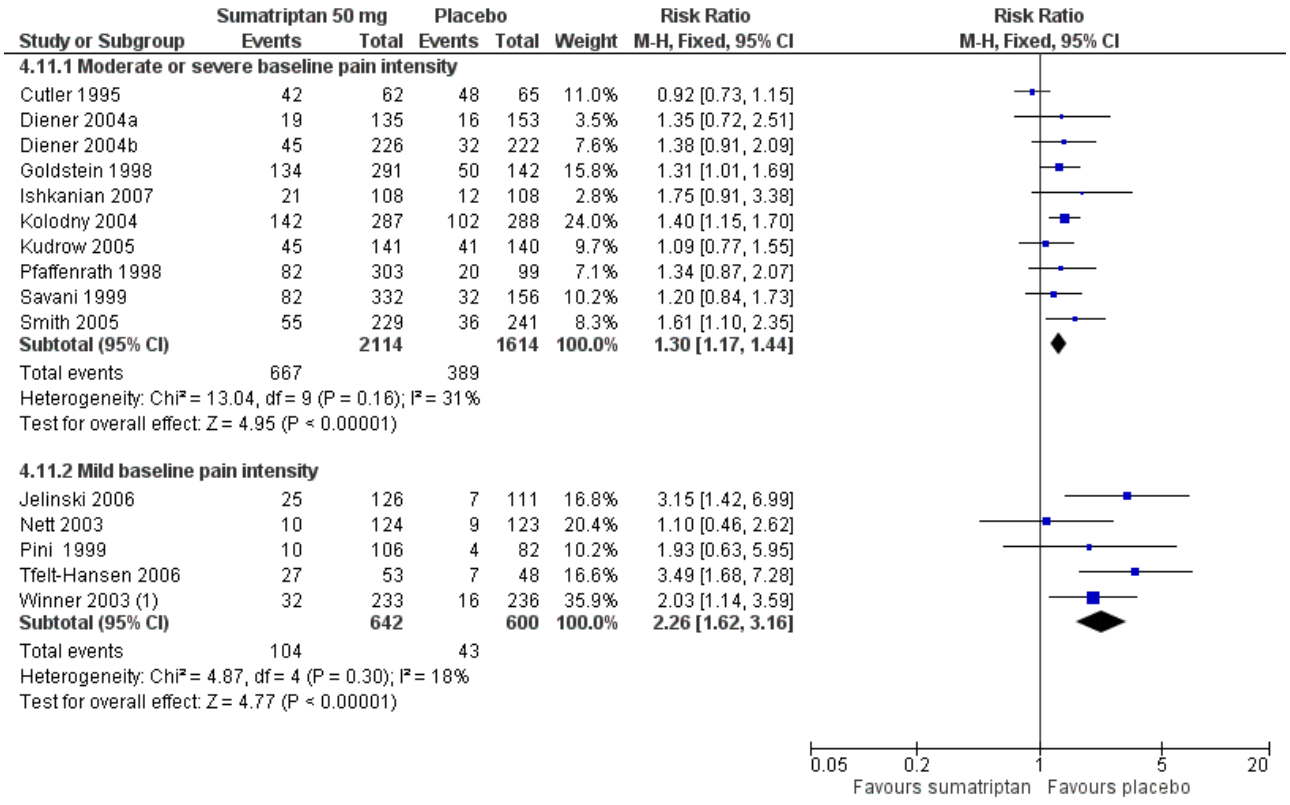
- The proportion of participants experiencing adverse events within 24 hours with sumatriptan 25 mg was 39% (371/956; range 24% to 71%).
- The proportion of participants experiencing adverse events within 24 hours with placebo was 37% (220/594; range 20% to 74%).
- The relative harm of treatment compared with placebo was 1.1 (1.0 to 1.3; Analysis 1.7); there was no significant difference between the two.

Sumatriptan 50 mg versus placebo

Ten studies (3728 participants) in participants with moderate or severe baseline pain intensity provided data (Cutler 1995; Diener 2004a; Diener 2004b; Goldstein 1998; Ishkanian 2007; Kolodny 2004; Kudrow 2005; Pfaffenrath 1998; Savani 1999; Smith 2005).

- The proportion of participants experiencing adverse events within 24 hours with sumatriptan 50 mg was 32% (667/2114; range 14% to 68%).
- The proportion of participants experiencing adverse events within 24 hours with placebo was 24% (389/1614; range 10% to 74%).
- The relative harm of treatment compared with placebo was 1.3 (1.2 to 1.4; Analysis 4.11; Figure 5); the NNH was 13 (9.7 to 22).

Figure 5. Forest plot of comparison: 4 Oral sumatriptan 50 mg versus placebo, outcome: 4.11 Any adverse event within 24 h.



Footnotes
(1) Data from Study 1 and Study 2 pooled

Sumatriptan 50 mg caused significantly more adverse events than sumatriptan 25 mg (z = 1.941; P = 0.052).

Six studies (1242 participants) in participants with mild baseline pain intensity provided data (Jelinski 2006; Nett 2003; Pini 1999; Tfelt-Hansen 2006; Winner 2003 Study 1 and Study 2).

- The proportion of participants experiencing adverse events within 24 hours with sumatriptan 50 mg was 16% (104/642; range 8% to 51%).
- The proportion of participants experiencing adverse events within 24 hours with placebo was 7% (43/600; range 5% to 15%).
- The relative harm of treatment compared with placebo was 2.3 (1.6 to 3.2; Analysis 4.11); the NNH was 11 (8.0 to 18).

Sumatriptan 100 mg versus placebo

Twelve studies (3257 participants) in participants with moderate or severe baseline pain intensity provided data (Cutler 1995; DKSMSG 1999; Dowson 2002; Ensink 1991; Geraud 2000; Goadsby 2000; Havanka 2000; Nappi 1994; Pfaffenrath 1998; Tfelt-Hansen 1995; Tfelt-Hansen 1998; Visser 1996).

- The proportion of participants experiencing adverse events within 24 hours with sumatriptan 100 mg was 43% (931/2171; range 22% to 64%).
- The proportion of participants experiencing adverse events within 24 hours with placebo was 23% (255/1086; range 6% to 74%).
- The relative harm of treatment compared with placebo was 1.7 (1.5 to 1.9; Analysis 12.11); the NNH was 5.2 (4.4 to 6.2).

Sumatriptan 100 mg caused significantly more adverse events than sumatriptan 50 mg (z = 5.379; P < 0.00006).

Four studies (941 participants) in participants with mild baseline pain intensity provided data (Jelinski 2006; Nett 2003; Winner 2003 Study 1 and Study 2).

- The proportion of participants experiencing adverse events within 24 hours with sumatriptan 100 mg was 19% (89/471; range 12% to 27%).
- The proportion of participants experiencing adverse events within 24 hours with placebo was 7% (32/470; range 6% to 8%).
- The relative harm of treatment compared with placebo was 2.8 (1.9 to 4.1; Analysis 12.11); the NNH was 8.3 (6.1 to 13).

Sumatriptan 25 mg versus rizatriptan 5 mg

Two studies (1169 participants) in participants with moderate or severe baseline pain intensity provided data (Goldstein 1998; Kolodny 2004).

- The proportion of participants experiencing adverse events within 24 hours with sumatriptan 25 mg was 43% (250/587; range 39% to 46%).
- The proportion of participants experiencing adverse events within 24 hours with rizatriptan 5 mg was 41% (238/582; range 38% to 44%).
- The relative harm of sumatriptan compared with rizatriptan was 1.0 (0.91 to 1.2; Analysis 2.5); there was no significant difference between the two treatments.

Sumatriptan 25 mg versus rizatriptan 10 mg

Two studies (1186 participants) in participants with moderate or severe baseline pain intensity provided data (Goldstein 1998; Kolodny 2004).

- The proportion of participants experiencing adverse events within 24 hours with sumatriptan 25 mg was 43% (250/587; range 39% to 46%).
- The proportion of participants experiencing adverse events within 24 hours with rizatriptan 10 mg was 46% (276/599; range 45% to 47%).
- The relative harm of sumatriptan compared with rizatriptan was 0.92 (0.81 to 1.1; Analysis 3.5); there was no significant difference between the two treatments.

Sumatriptan 50 mg versus effervescent acetylsalicylic acid 1000 mg

Two studies (730 participants) in participants with moderate or severe baseline pain intensity provided data (Diener 2004a; Diener 2004b).

- The proportion of participants experiencing adverse events within 24 hours with sumatriptan 50 mg was 18% (64/361; range 14% to 20%).
- The proportion of participants experiencing adverse events within 24 hours with effervescent ASA 1000 mg was 15% (55/369; range 13% to 16%).
- The relative harm of sumatriptan compared with effervescent ASA was 1.2 (0.85 to 1.6; Analysis 5.5); there was no significant difference between the two treatments.

Sumatriptan 50 mg versus zolmitriptan 2.5 mg

Two studies (1771 participants) in participants with moderate or severe baseline pain intensity provided data (Gallagher 2000; Gruffyd-Jones 2001).

- The proportion of participants experiencing adverse events within 24 hours with sumatriptan 50 mg was 32% (290/893; range 29% to 34%).
- The proportion of participants experiencing adverse events within 24 hours with zolmitriptan 2.5 mg was 32% (283/878; range 28% to 35%).
- The relative harm of sumatriptan compared with zolmitriptan was 1.0 (0.88 to 1.2; Analysis 6.3); there was no significant difference between the two treatments.

Sumatriptan 50 mg versus zolmitriptan 5 mg

Two studies (1790 participants) in participants with moderate or severe baseline pain intensity provided data (Gallagher 2000; Gruffyd-Jones 2001).

- The proportion of participants experiencing adverse events within 24 hours with sumatriptan 50 mg was 32% (290/893; range 29% to 34%).
- The proportion of participants experiencing adverse events within 24 hours with zolmitriptan 5 mg was 36% (322/897; range 33% to 38%).
- The relative harm of sumatriptan compared with zolmitriptan was 0.91 (0.80 to 1.0; Analysis 7.3); there was no significant difference between the two treatments.

Sumatriptan 50 mg versus rizatriptan 5 mg

Two studies (1160 participants) in participants with moderate or severe baseline pain intensity provided data (Goldstein 1998; Kolodny 2004).

- The proportion of participants experiencing adverse events within 24 hours with sumatriptan 50 mg was 48% (276/578; range 46% to 49%).
- The proportion of participants experiencing adverse events within 24 hours with rizatriptan 5 mg was 41% (238/582; range 38% to 44%).
- The relative harm of sumatriptan compared with rizatriptan was 1.2 (1.0 to 1.3; Analysis 8.5); there was no significant difference between the two treatments.

Sumatriptan 50 mg versus rizatriptan 10 mg

Two studies (1177 participants) in participants with moderate or severe baseline pain intensity provided data (Goldstein 1998; Kolodny 2004).

- The proportion of participants experiencing adverse events within 24 hours with sumatriptan 50 mg was 48% (276/578; range 46% to 49%).
- The proportion of participants experiencing adverse events within 24 hours with rizatriptan 10 mg was 46% (276/599; range 45% to 47%).
- The relative harm of sumatriptan compared with rizatriptan was 1.0 (0.92 to 1.2; Analysis 9.5); there was no significant difference between the two treatments.

Sumatriptan 100 mg versus rizatriptan 10 mg

Two studies (856 participants) in participants with moderate or severe baseline pain intensity provided data (Tfelt-Hansen 1998; Visser 1996).

- The proportion of participants experiencing adverse events within 24 hours with sumatriptan 100 mg was 52% (217/421; range 45% to 52%).
- The proportion of participants experiencing adverse events within 24 hours with rizatriptan 10 mg was 47% (203/435; range 47% to 48%).
- The relative harm of sumatriptan compared with rizatriptan was 1.1 (0.96 to 1.3; Analysis 15.3); there was no significant difference between the two treatments.

Sumatriptan 100 mg versus acetylsalicylic acid 900 mg + metoclopramide 10 mg

Two studies (621 participants) in participants with moderate or severe baseline pain intensity provided data (Tfelt-Hansen 1995; Thomson 1992).

- The proportion of participants experiencing adverse events within 24 hours with sumatriptan 100 mg was 37% (112/300; range 30% to 42%).
- The proportion of participants experiencing adverse events within 24 hours with ASA 900 mg + MCP 10 mg was 24% (78/321; range 18% to 29%).
- The relative harm of sumatriptan compared with ASA + MCP was 1.5 (1.2 to 1.9; Analysis 18.4); the NNH was 7.7 (4.9 to 17).

Summary of results E: Number of participants experiencing any adverse event within 24 hours of study treatment

Comparison	Studies	Participants	Treatment (%)	Comparator (%)	Relative risk (95% CI)	NNH (95% CI)
Sumatriptan 25 mg versus placebo	4	1550	39	37	1.1 (1.0 to 1.3)	Not calculated
Sumatriptan 50 mg versus placebo (in participants with moderate or severe baseline pain intensity)	10	3728	32	24	1.3 (1.2 to 1.4)	13 (9.7 to 22)
Sumatriptan 50 mg versus placebo (in participants with mild baseline pain intensity)	6	1242	16	7	2.3 (1.6 to 3.2)	11 (8.0 to 18)
Sumatriptan 100 mg versus placebo (in participants with moderate or severe baseline pain intensity)	12	3257	43	23	1.7 (1.5 to 1.9)	5.2 (4.4 to 6.2)
Sumatriptan 100 mg versus placebo (in participants with mild baseline pain intensity)	4	941	19	7	2.8 (1.9 to 4.1)	8.3 (6.1 to 13)
Sumatriptan 25 mg versus rizatriptan 5 mg	2	1169	43	41	1.0 (0.91 to 1.2)	Not calculated

Sumatriptan 25 mg versus rizatriptan 10 mg	2	1186	43	46	0.92 (0.81 to 1.1)	Not calculated
Sumatriptan 50 mg versus effervescent ASA 1000 mg	2	730	18	15	1.2 (0.85 to 1.6)	Not calculated
Sumatriptan 50 mg versus zolmitriptan 2.5 mg	2	1771	32	32	1.0 (0.88 to 1.2)	Not calculated
Sumatriptan 50 mg versus zolmitriptan 5 mg	2	1790	32	36	0.91 (0.80 to 1.0)	Not calculated
Sumatriptan 50 mg versus rizatriptan 5 mg	2	1160	48	41	1.2 (1.0 to 1.3)	Not calculated
Sumatriptan 50 mg versus rizatriptan 10 mg	2	1177	48	46	1.0 (0.92 to 1.2)	Not calculated
Sumatriptan 100 mg versus rizatriptan 10 mg	2	856	52	47	1.1 (0.96 to 1.3)	Not calculated
Sumatriptan 100 mg versus ASA 900 mg + MCP 10 mg	2	621	37	24	1.5 (1.2 to 1.9)	7.7 (4.9 to 17)

Summary of results F: Statistical tests for the effect of dose and baseline pain intensity

	z	P
Sumatriptan 25 mg versus 50 mg	1.941	0.052
Sumatriptan 50 mg versus 100 mg	5.379	<0.00006

There was a clear dose response relationship for sumatriptan in comparisons with placebo, with significantly more participants experiencing adverse events with each dose increment (NNHs of 5.2, 13, and 'not statistically significant' for sumatriptan 100 mg, 50 mg, and 25 mg, respectively). There was no significant difference between sumatriptan 25 mg, 50 mg, or 100 mg and rizatriptan at either 5 mg or 10 mg. Likewise there was no significant difference in incidence of adverse events within 24 hours between sumatriptan 50 mg and effervescent ASA 1000 mg, or zolmitriptan 2.5 mg and 5 mg. Only in the comparison between sumatriptan 100 mg and ASA 900 mg + MCP 10 mg was sumatriptan significantly worse than its comparator (NNH of 7.7).

Sensitivity analyses

We carried out sensitivity analyses to take into consideration and assess the effect of including adverse event data collected from participants who may have had more than one dose of study medication. Where there were sufficient data based on only a single dose to provide a meaningful analysis, we performed sensitivity analyses simply to remove the potentially contaminated data.

Sumatriptan 25 mg versus placebo

Of the four studies originally analysed comparing sumatriptan 25 mg with placebo for incidence of any adverse event within 24 hours, one offered participants a second dose of study medication (Pfaffenrath 1998). Removing this study from the analysis made no significant difference to the calculated relative risk of treatment versus placebo (analysis not shown).

Sumatriptan 50 mg versus placebo

Of the 10 studies originally analysed comparing sumatriptan 50 mg with placebo for incidence of any adverse event within 24 hours, three offered participants a second dose of study medication (Kudrow 2005; Pfaffenrath 1998; Savani 1999). Removing these studies from the analysis made no significant difference to the calculated relative risk of treatment versus placebo (analysis not shown).

Sumatriptan 100 mg versus placebo

Of the 12 studies originally analysed comparing sumatriptan 50 mg with placebo for incidence of any adverse event within 24 hours, four offered participants a second dose of study medication and did not report adverse events according to the number

of doses received (Dowson 2002; Ensink 1991; Goadsby 2000; Pfaffenrath 1998). Removing these studies from the analysis made no significant difference to the calculated relative risk of treatment versus placebo (analysis not shown).

Participants experiencing specific adverse events

Six studies did not report on the incidence of individual adverse events (Diener 2004b; Dodick 2002; Goadsby 1991; Lines 2001; Lipton 2000; Sandrini 2007), and a further four studies reported only the incidence of events by body system affected (Bussone 2000; Diener 2004a; Goldstein 2005; Pini 1999). The remaining 51 studies reported the incidence of at least one specific adverse event, although there was significant variability in the manner of reporting that further limited the number of studies providing data for pooled analyses. Two studies (Latere 1991; Myllyla 1998) reported the number of events, rather than the number of participants experiencing an event in each treatment arm, and therefore did not provide data for analysis. One study (Tfelt-Hansen 2006) reported only the total number of participants experiencing a specific adverse event, and did not break this down by treatment arm. As discussed previously, the duration over which adverse event data were collected varied between studies and, as with the total incidence of adverse events, 11 studies (160-104; Dahlof 2009; GL/MIG/001/92; GL/MIG/001A/92; GL/MIG/002; GL/MIG/002A; Mathew 2003; Pini 1995; Sargent 1995; Sheftell 2005 Study 1 and Study 2) were not included in pooled analyses due to inappropriate collection periods.

Individual adverse events were reported inconsistently between studies. The majority of studies reported only the most commonly occurring adverse events, for example those occurring in more than 3% of participants in any of the treatment arms, while others used different terms to describe the same or similar events. In order to be as inclusive as possible we have pooled related adverse events into groups (described in detail in Appendix 8). Where one study provided data on more than one event in a particular group, for example reporting both malaise/fatigue and asthenia, we have counted the event with the higher incidence and ignored the other in order not to double count participants, because it is possible that any one participant may have experienced both events. This will lead to an underestimation of incidence if all those with the less frequent event did not also have the more frequent one. Since there were no significant differences in the overall incidence of adverse events between participants treating attacks of mild baseline pain intensity and participants treating attacks of moderate or severe intensity, we performed analysis of individual adverse events on all participants, regardless of pain intensity at baseline.

One final limitation of these analyses was that a significant proportion of studies reported only events judged to be related to the study medication. In these cases it was not clear whether it was the event, in general terms, that was judged to be related, or whether it was a specific event in a specific patient. The latter may provide an underestimate of the incidence of this event in the study population as a whole, and therefore the results should be interpreted cautiously.

Where two or more placebo-controlled studies reported data for at least 200 participants investigating the incidence of a specific adverse event within 24 hours of study treatment, we carried out pooled analysis to calculate the relative risk, and where appropriate the NNH (Summary of results G; Analysis 1.8; Analysis 4.12; Analysis 12.12; Analysis 19.3; Analysis 20.2).

Summary of results G: Number of participants experiencing specific adverse events within 24 hours of study treatment in placebo-controlled studies

	Studies	Participants treated	Treatment (%)	Placebo (%)	Relative risk (95% CI)	NNH (95% CI)
Malaise/fatigue/asthenia						
Sumatriptan 25 mg	3	1419	3	2	2.6 (1.2 to 5.8)	51 (28 to 260)
Sumatriptan 50 mg	10	3689	3	1	2.7 (1.6 to 4.5)	47 (33 to 85)
Sumatriptan 100 mg	16	4844	6	2	2.4 (1.6 to 3.4)	25 (20 to 35)
Dizziness/vertigo						
Sumatriptan 25 mg	4	1550	4	5	0.99 (0.61 to 1.6)	Not calculated
Sumatriptan 50 mg	13	4211	5	3	1.8 (1.3 to 2.5)	49 (31 to 110)
Sumatriptan 100 mg	17	4959	5	2	2.3 (1.6 to 3.4)	29 (22 to 41)
Nausea/vomiting						
Sumatriptan 25 mg	4	1550	5	6	1.1 (0.74 to 1.8)	Not calculated

Sumatriptan 50 mg	13	3799	4	3	1.4 (0.97 to 2.0)	Not calculated
Sumatriptan 100 mg	20	5284	7	4	1.7 (1.3 to 2.2)	35 (25 to 61)
Sumatriptan 200 mg	3	681	17	5	3.2 (1.9 to 5.4)	8.5 (6.1 to 14)
Sumatriptan 300 mg	2	624	15	5	2.9 (1.6 to 5.2)	10 (7.0 to 19)
Mouth disorder/disturbance of taste						
Sumatriptan 25 mg	3	1148	5	6	0.82 (0.49 to 1.4)	Not calculated
Sumatriptan 50 mg	5	1887	5	4	1.4 (0.90 to 2.1)	Not calculated
Sumatriptan 100 mg	5	1047	6	4	1.4 (0.78 to 2.4)	Not calculated
Sumatriptan 200 mg	2	605	8	3	3.0 (1.3 to 6.7)	18 (11 to 50)
Sumatriptan 300 mg	2	624	15	3	5.5 (2.6 to 12)	8.1 (6.0 to 12)
Chest pain/symptoms						
Sumatriptan 25 mg	3	1419	2	1	1.8 (0.70 to 4.3)	Not calculated
Sumatriptan 50 mg	7	2673	3	1	2.1 (1.1 to 3.9)	69 (40 to 260)
Sumatriptan 100 mg	12	3452	3	1	3.0 (1.7 to 5.4)	44 (31 to 73)
Sumatriptan 200 mg	2	605	1	0	4.4 (0.54 to 36)	Not calculated
Sumatriptan 300 mg	2	624	6	0	17 (2.4 to 127)	16 (11 to 27)
Heat sensations/flushing						
Sumatriptan 50 mg	4	1515	3	1	3.8 (1.5 to 9.6)	49 (30 to 130)
Sumatriptan 100 mg	2	786	5	1	3.6 (0.68 to 19)	Not calculated
Palpitations/tachycardia						
Sumatriptan 100 mg	2	499	3	1	3.5 (0.75 to 17)	Not calculated
Diarrhoea						
Sumatriptan 50 mg	3	1327	4	1	2.5 (1.2 to 5.3)	46 (26 to 210)
Feeling of heaviness/tightness						
Sumatriptan 50 mg	5	1179	2	0	3.0 (0.88 to 10)	Not calculated
Sumatriptan 100 mg	6	1317	4	0	4.1 (1.3 to 13)	26 (18 to 46)
Paraesthesia/numbness						
Sumatriptan 25 mg	3	1148	4	1	3.4 (1.4 to 8.4)	36 (22 to 100)

Sumatriptan 50 mg	10	3089	2	1	2.7 (1.4 to 5.0)	66 (42 to 160)
Sumatriptan 100 mg	13	3154	5	1		27 (21 to 37)
Sumatriptan 200 mg	2	605	3	0	5.1 (0.92 to 28)	Not calculated
Sumatriptan 300 mg	2	624	6	0	9.9 (1.9 to 51)	19 (13 to 38)
Headache						
Sumatriptan 25 mg	3	1148	5	4	1.1 (0.67 to 1.9)	Not calculated
Sumatriptan 50 mg	5	1904	4	3	1.3 (0.82 to 2.1)	Not calculated
Sumatriptan 100 mg	3	411	6	10	0.77 (0.41 to 1.4)	Not calculated
Drowsiness/somnolence						
Sumatriptan 25 mg	3	1148	5	5	0.91 (0.53 to 1.6)	Not calculated
Sumatriptan 50 mg	9	2628	4	3	1.4 (0.87 to 2.1)	Not calculated
Sumatriptan 100 mg	14	3710	4	2	1.5 (1.0 to 2.3)	53 (33 to 130)
Sumatriptan 200 mg	2	605	5	1	6.2 (1.4 to 27)	25 (15 to 64)
Sumatriptan 300 mg	2	624	5	1	6.9 (1.6 to 29)	22 (14 to 48)
Abdominal pain/discomfort/dyspepsia						
Sumatriptan 100 mg	5	1357	5	2	3.0 (1.4 to 6.3)	32 (20 to 76)
Anxiety						
Sumatriptan 50 mg	2	518	1	0	1.9 (0.36 to 9.9)	Not calculated
Sumatriptan 100 mg	2	499	1	0	1.9 (0.36 to 9.9)	Not calculated
Neck/back pain						
Sumatriptan 50 mg	2	364	1	2	0.49 (0.09 to 2.7)	Not calculated
Sumatriptan 100 mg	6	1508	3	1	1.9 (0.73 to 4.7)	Not calculated

We also analysed studies for the incidence of specific adverse events in sumatriptan versus active comparators and, where appropriate, calculated NNHs (Appendix 9). For the majority of adverse events there was no significant difference between sumatriptan and the comparator. Sumatriptan 100 mg was found to cause significantly fewer occurrences of malaise/fatigue/asthenia and nausea/vomiting than eletriptan 80 mg (NNHs of -17 and -24 respectively). Sumatriptan 25 mg caused fewer occurrences of dizziness/vertigo and drowsiness/somnolence than rizatriptan 10 mg (NNHs of -20 and -34 respectively). Conversely, sumatriptan 50 mg caused significantly more headache than rizatriptan of either 5 or 10 mg (NNHs of 38 and 34 respectively), while sumatriptan 100 mg caused significantly more nausea/vomiting, chest pain/symptoms, feeling of heaviness/tightness, and paraesthesia/numbness than ASA 900 mg + MCP 10 mg (NNHs of 19, 33, 33, and 37 respectively).

Participants experiencing serious adverse events

Twenty-five studies did not specifically comment on serious adverse events (Cutler 1995; Diener 2004a; Dodick 2002; Dowson 2002; Ensink 1991; Freitag 2001; GL/MIG/001/92; GL/MIG/001A/92; GL/MIG/002; GL/MIG/002A; Goadsby 1991; Goadsby 2000; Havanka 2000; Ishkanian 2007; Kolodny 2004; Kudrow 2005; Lines 2001;

Myllyla 1998; Nappi 1994; Patten 1991; Pfaffenrath 1998; Pini 1995; Sargent 1995; Tfelt-Hansen 2006; Thomson 1992), 15 studies reported that there were none during the study (Bussone 2000; Carpay 2004; DKSMSG 1999; Goldstein 2005; Gruffyd-Jones 2001; Jelinski 2006; Kaniecki 2006; Nett 2003; Pini 1999; Schulman 2003; Smith 2005; Spierings 2001; Tfelt-Hansen 1998; Winner 2003 Study 1 and Study 2), and six reported that there were no drug-related serious adverse events (Geraud 2000; Goldstein 1998; Mathew 2003; Sandrini 2002; Sheftell 2005 Study 1 and Study 2). The remaining 15 studies all reported at least one serious adverse event, although most were judged to be unrelated to any study medication.

In studies reporting occurrence of serious adverse events separately for sumatriptan and comparator treatment arms (160-104; Banerjee 1992; Brandes 2007; Dahlof 1991; Diener 2004b; GL/MIG/009; Latere 1991; Sandrini 2007; Visser 1996), or the absence of such events (Bussone 2000; Carpay 2004; DKSMSG 1999; Goldstein 2005; Gruffyd-Jones 2001; Jelinski 2006; Kaniecki 2006; Nett 2003; Pini 1999; Schulman 2003; Smith 2005; Spierings 2001; Tfelt-Hansen 1998; Winner 2003 Study 1 and Study 2), the incidence was less than 1% in any treatment arm, except three (160-104 placebo group, 2/93 treated participants; Banerjee 1992 placebo group, 1/39 treated participants; Visser 1996 rizatriptan 20 mg group, 1/82 treated participants).

Sumatriptan versus placebo

Eighteen studies (7687 participants) provided data on sumatriptan of any dose versus placebo (160-104; Banerjee 1992; Brandes 2007 Study 1 and Study 2; Bussone 2000; Carpay 2004; Dahlof 1991; Diener 2004b; DKSMSG 1999; Goldstein 2005; Jelinski 2006; Kaniecki 2006; Nett 2003; Pini 1999; Smith 2005; Tfelt-Hansen 1998; Visser 1996; Winner 2003 Study 1 and Study 2).

The overall incidence of serious adverse events was 0.12% (6/4829) for all doses of sumatriptan (including second doses and rescue medication), and 0.10% (3/2858) for placebo. There were too few events to calculate relative risk or NNH. Further details of individual studies are in Appendix 7.

Sumatriptan versus active comparators

Sixteen studies (11,599 participants/attacks) provided data on sumatriptan of any dose versus active comparators (160-104; Brandes 2007 Study 1 and Study 2; Diener 2004b; DKSMSG 1999; Gallagher 2000; GL/MIG/009; Goldstein 2005; Gruffyd-Jones 2001; Latere 1991; Sandrini 2007; Schulman 2003; Smith 2005; Spierings 2001; Tfelt-Hansen 1998; Visser 1996). In all cases there were too few events to calculate relative risk or NNH.

Three studies (1946 participants) comparing sumatriptan with naproxen provided data (Brandes 2007 Study 1 and Study 2; Smith 2005). The overall incidence was 0.10% (1/964) for all doses of sumatriptan (50 to 85 mg), and 0% (0/982) for naproxen (500 mg).

Three studies (1952 participants) comparing sumatriptan with sumatriptan + naproxen provided data (Brandes 2007 Study 1 and Study 2; Smith 2005). The overall incidence was 0.10% (1/964) for all doses of sumatriptan (50 to 85 mg), and 0% (0/988) for sumatriptan + naproxen (50-85/500 mg).

Two studies (2878 participants/attacks) comparing sumatriptan with zolmitriptan provided data (Gallagher 2000; Gruffyd-Jones 2001). The overall incidence was 0.51% (6/1167) for all doses of sumatriptan (25 to 50 mg), and 0.23% (4/1711) for all doses of zolmitriptan (2.5 to 5 mg).

Two studies (1303 participants) comparing sumatriptan with rizatriptan provided data (Tfelt-Hansen 1998; Visser 1996). The overall incidence was 0% (0/460) for sumatriptan (100 mg), and 0.12% (1/843) for all doses of rizatriptan (5 to 40 mg).

Withdrawals due to adverse events

Thirty studies did not specifically report on adverse event withdrawals or did not report data for each treatment arm separately. The remaining 31 studies reported the number of withdrawals due to adverse events per treatment group (160-104; Banerjee 1992; Dahlof 1991; Dahlof 2009; DKSMSG 1999; Dowson 2002; Gallagher 2000; GL/MIG/001/92; GL/MIG/001A/92; GL/MIG/002; GL/MIG/002A; GL/MIG/009; Goadsby 2000; Goldstein 1998; Gruffyd-Jones 2001; Havanka 2000; Latere 1991; Nappi 1994; Nett 2003; Patten 1991; Pfaffenrath 1998; Sandrini 2002; Sandrini 2007; Sargent 1995; Sheftell 2005 Study 1 and Study 2; Spierings 2001; Tfelt-Hansen 1995; Tfelt-Hansen 1998; Thomson 1992; Visser 1996). Some of these studies either did not report how multiple attacks were combined or reported only drug-related adverse event withdrawals, but were included anyway in order to be more inclusive and conservative.

In studies reporting the occurrence of adverse event withdrawals, nine reported none (Dahlof 2009; Dowson 2002; Havanka 2000; Nett 2003; Sargent 1995; Sheftell 2005 Study 1 and Study 2; Spierings 2001; Visser 1996), four reported an incidence in any treatment arm of less than 2% (DKSMSG 1999; Goadsby 2000; Goldstein 1998; Tfelt-Hansen 1998), 12 reported an incidence in any treatment arm of less than 5% (Gallagher 2000; GL/MIG/001A/92; GL/MIG/002; GL/MIG/002A; Gruffyd-Jones 2001; Latere 1991; Nappi 1994; Pfaffenrath 1998; Sandrini 2002; Sandrini 2007; Tfelt-Hansen 1995; Thomson 1992), and six studies reported an incidence of greater than 5% in at least one treatment arm (160-104; Banerjee 1992; Dahlof 1991; GL/MIG/001/92; GL/MIG/009; Patten 1991).

Sumatriptan versus placebo

Nineteen studies (10,059 participants) provided data on sumatriptan of any dose versus placebo (160-104; Banerjee 1992; Dahlof 1991; Dahlof 2009; DKSMSG 1999; Dowson 2002; Goadsby 2000; Goldstein 1998; Havanka 2000; Nappi 1994; Nett 2003; Patten 1991; Pfaffenrath 1998; Sandrini 2002; Sargent 1995; Sheftell 2005; Tfelt-Hansen 1995; Tfelt-Hansen 1998; Visser 1996).

The overall incidence of adverse event withdrawal was 1.6% (113/7133) for all doses of sumatriptan (including second doses and rescue medication), and 0.65% (19/2926) for placebo. If studies using initial doses of sumatriptan of greater than 100 mg were removed from this analysis, the overall incidence of adverse event withdrawal was 0.71% (45/6349) for all doses of sumatriptan ≤ 100 mg. A total of 1041 participants provided data comparing sumatriptan > 100 mg with placebo, giving an NNH of 14 (10 to 23) for treatment with sumatriptan. Other than for doses > 100 mg there was no evidence of a dose response relationship, and there were too few events to calculate relative risk or NNH. Further details of individual studies are in Appendix 7.

Sumatriptan versus active comparators

Twenty-two studies (15,099 participants) provided data on sumatriptan of any dose versus active comparators (160-104; Dahlof 2009; DKSMSG 1999; Dowson 2002; Gallagher 2000; GL/MIG/001/92; GL/MIG/001A/92; GL/MIG/002; GL/MIG/002A; GL/MIG/009; Goadsby 2000; Goldstein 1998; Gruffyd-Jones 2001; Havanka 2000; Latere 1991; Sandrini 2002; Sandrini 2007; Spierings 2001; Tfelt-Hansen 1995; Tfelt-Hansen 1998; Thomson 1992; Visser 1996). In all cases there were too few events to calculate relative risk or NNH.

Two studies (1742 participants) comparing sumatriptan 50 mg or 100 mg with almotriptan 12.5 mg or 25 mg provided data (Dowson 2002; Spierings 2001). Neither trial reported any withdrawals due to adverse events.

Two studies (3004 participants/attacks) comparing sumatriptan 25 mg or 50 mg with zolmitriptan 2.5 mg or 5 mg provided data (Gallagher 2000; Gruffyd-Jones 2001). The overall incidence was 2.5% (31/1229) for all doses of sumatriptan, and 2.9% (52/1775) for all doses of zolmitriptan.

Two studies (1328 participants) comparing sumatriptan 100 mg with paracetamol 100 mg + MCP 10 mg provided data (GL/MIG/001/92; GL/MIG/001A/92). The overall incidence was 4.7% (31/653) for sumatriptan, and 1.9% (13/675) for paracetamol + MCP.

Two studies (1426 participants) comparing sumatriptan 100 mg with buclizine hydrochloride 12.5 mg + paracetamol 1000 mg + codeine phosphate 16 mg (Migraleve) provided data (GL/MIG/002; GL/MIG/002A). The overall incidence was 4.6% (33/716) for sumatriptan, and 1.7% (12/710) for Migraleve.

Three studies (1779 participants) comparing sumatriptan 25 mg, 50 mg, or 100 mg with eletriptan 20 mg, 40 mg, or 80 mg provided data (160-104; Goadsby 2000; Sandrini 2002). The overall incidence was 1.2% (10/841) for sumatriptan, and 1.3% (12/938) for eletriptan.

Three studies (2482 participants) comparing sumatriptan 25 mg, 50 mg, or 100 mg with rizatriptan 5 mg or 10 mg provided data (Goldstein 1998; Tfelt-Hansen 1998; Visser 1996). The overall incidence was 0.38% (4/1048) for sumatriptan, and 0.28% (4/1434) for rizatriptan.

Two studies (621 participants) comparing sumatriptan 100 mg with ASA 900 mg + MCP 10 mg provided data (Tfelt-Hansen 1995; Thomson 1992). The overall incidence was 3.0% (9/300) for sumatriptan, and 0.31% (1/321) for ASA + MCP.

Consistency of response

Of the 27 included studies that involved participants treating more than one migraine attack, 13 provided some data on consistency of response to treatment across successive attacks. Consistency was addressed in two distinct ways in these 13 studies. Twelve studies (Bussone 2000; Gallagher 2000; GL/MIG/001/92; GL/MIG/001A/92; GL/MIG/002; GL/MIG/002A; GL/MIG/009; Gruffyd-Jones 2001; Myllyla 1998; Pfaffenrath 1998; Tfelt-Hansen 1995; Thomson 1992) reported the proportion of participants achieving a particular outcome (responding) for each successive attack separately, thereby providing a measure of the consistency of the population's response to treatment over successive attacks. Four studies (Gallagher 2000; Gruffyd-Jones 2001; Pfaffenrath 1998; Sandrini 2002) reported on the proportion of participants achieving a particular outcome in a defined fraction (for example in two-thirds) of their treated attacks. This provides a measure of the consistency of an individual's response to treatment over successive attacks.

Eight studies (GL/MIG/001/92; GL/MIG/001A/92; GL/MIG/002; GL/MIG/002A; Myllyla 1998; Pfaffenrath 1998; Tfelt-Hansen 1995; Thomson 1992) provided separate data for the proportion of participants achieving headache relief at two hours with sumatriptan 100 mg in up to three successive attacks. Response rates ranged from 39% to 79% for an individual attack. There were no clear trends over successive attacks in the same study (Figure 6), suggesting that the proportion of participants achieving headache relief at two hours was consistent. Results for headache relief at two hours in participants with other doses of sumatriptan were similar and, in fact, no efficacy outcome for which data over successive attacks were reported separately showed any evidence of an inconsistent response. One study (Gallagher 2000) provided data on the incidence of adverse events over the course of six treated attacks. In this case, for both the 25 mg and 50 mg doses of sumatriptan, the proportion of participants experiencing an adverse event within 24 hours appeared to decrease as successive attacks were treated (Figure 7), such that the incidence of adverse events was much lower in participants treating their sixth attack than those treating their first.

Figure 6. Consistency of response: proportion of participants treated with sumatriptan 100 mg achieving headache relief at 2 hours over successive attacks

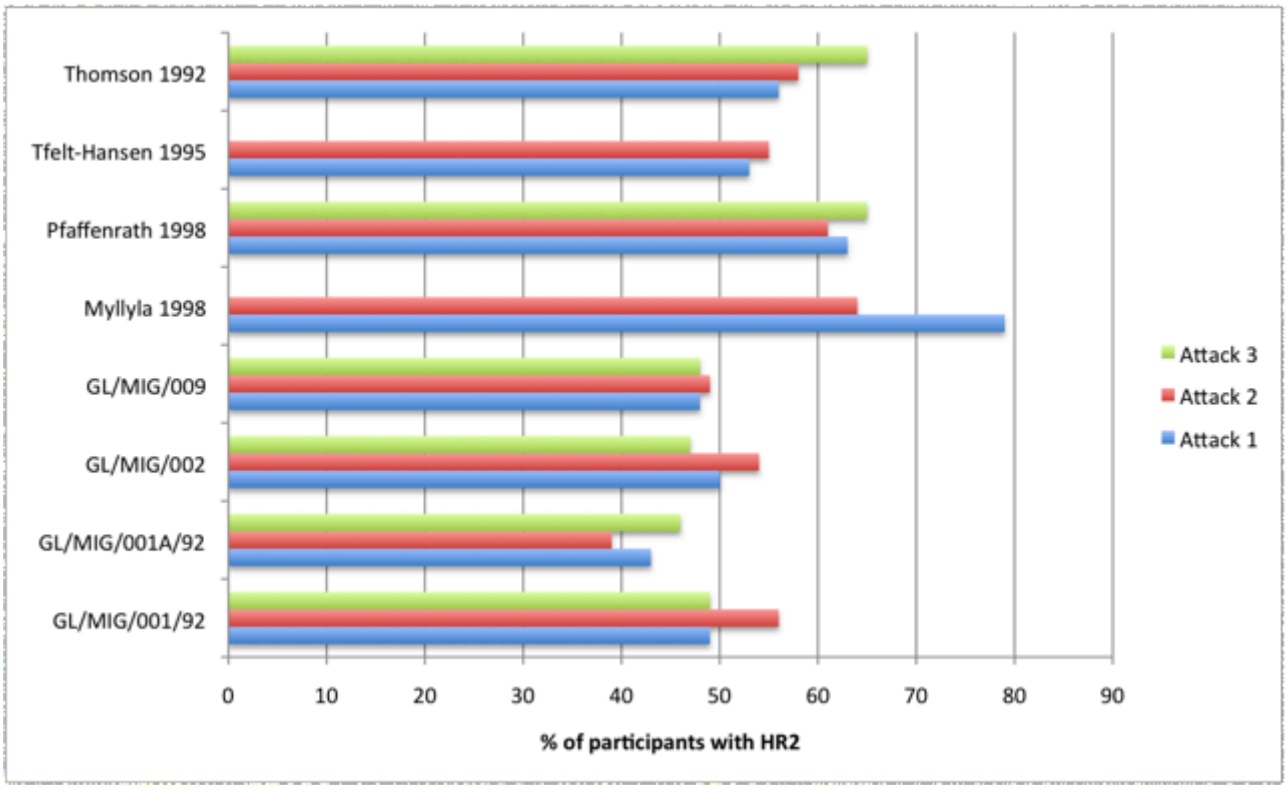
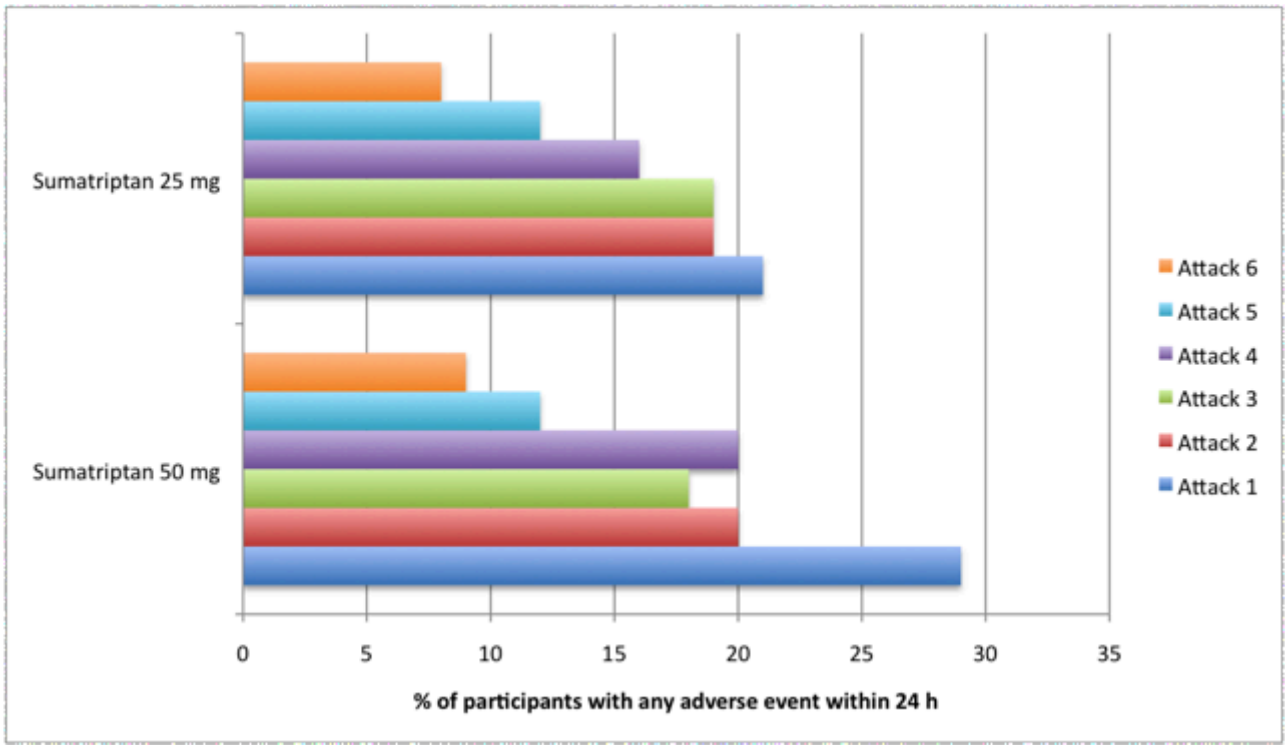


Figure 7. Consistency of response: proportion of participants treated with sumatriptan 25 mg or 50 mg experiencing any adverse events within 24 hours over successive attacks (data from Gallagher 2000)



Two studies (Pfaffenrath 1998; Sandrini 2002) reported the percentage of participants achieving headache relief at two hours in two-thirds or more of their treated attacks. Approximately 50% of participants treated with sumatriptan 25 mg responded to treatment in at least 2/3 attacks, while about 55% did so when treated with sumatriptan 50 mg, and about 60% when treated with sumatriptan 100 mg. Two studies (Gallagher 2000; Gruffyd-Jones 2001) reported the percentage of participants achieving headache relief at two hours in 80% or more of their treated attacks. Again, the lower dose of 25 mg resulted in a smaller fraction of participants achieving this level of consistency than the 50 mg dose (approximately 30% with sumatriptan 25 mg and 40% with sumatriptan 50 mg). Finally one study (Sandrini 2002) reported the proportion of participants experiencing headache relief at two hours in 3/3 of their treated attacks (i.e. 100%). Twenty-two percent of participants treated with sumatriptan 50 mg achieved headache relief at two hours in every attack treated, while 24% of those treated with sumatriptan 100 mg did so.

DISCUSSION

Summary of main results

This review included 61 randomised, double-blind, controlled studies with 37,250 participants. Twenty-four studies had only a placebo control, 13 had only active comparators, and 24 had both placebo and active comparators. Active comparators were isometheptene mucate + dichloralphenazone + acetaminophen, zolmitriptan, rizatriptan, tonabersat, effervescent acetylsalicylic acid, ibuprofen, paracetamol (acetaminophen) + aspirin + caffeine, valdecoxib, eletriptan, indomethacin + prochlorperazine + caffeine (Indoprocaf), sumatriptan + metoclopramide, sumatriptan + naproxen, naproxen, almotriptan, diclofenac potassium, naratriptan, ergotamine tartrate + caffeine (Cafergot), tolfenamic acid, acetylsalicylic acid + metoclopramide, buclizine hydrochloride + paracetamol + codeine phosphate (Migraleve), and ergotamine tartrate + cyclizine hydrochloride + caffeine hydrate (Migril). Sumatriptan was studied in doses of 25, 50, 85, 100, 200, and 300 mg in an oral tablet (either standard or disintegrating) formulation. Most of the data were for the 50 mg and 100 mg doses. In most studies participants treated established attacks of moderate to severe intensity, but some treated when pain was still mild. Separate analyses were carried out for these different levels of baseline pain.

For nearly all efficacy outcomes, sumatriptan of any dose was superior to placebo and gave clinically useful numbers needed to treat (NNTs), the one exception to this being pain-free at one hour. The remarkably consistent response between studies for the primary outcomes, as illustrated by L'Abbé plots (Appendix 10), was not unexpected given the inclusion criteria for the studies and the well-defined outcomes. There was a trend for lower (better) NNTs at higher doses, with significant differences between 50 mg and 100 mg for pain-free and headache relief at two hours, and sustained pain-free during the 24 hours postdose; and between 100 mg and 200 mg for headache relief at two hours. Where treatment of participants with mild baseline pain was compared with treatment at moderate or severe baseline pain, treatment while pain was still mild was found to be significantly more effective for outcomes of pain-free at two hours and sustained pain-free during 24 hours.

For the International Headache Society (IHS)-preferred outcome of pain-free at two hours, sumatriptan 25 mg, 50 mg, and 100 mg compared with placebo gave NNTs of 6.2, 6.1, and 4.7, respectively, in participants treating established attacks with moderate or severe pain. In participants treating attacks while pain was still mild, sumatriptan 50 mg and 100 mg compared with placebo gave NNTs of 4.4 and 3.0, respectively. About 30% of participants with moderate or severe baseline pain were responders with sumatriptan compared to 10% with placebo, while response rates were higher for participants with mild baseline pain (about 45% to 60% responders with sumatriptan compared to 24% with placebo). For pain-free at one hour in participants with moderate or severe baseline pain, the NNTs were 33 and 18 for sumatriptan 50 mg and 100 mg, respectively (5% to 7% responders with sumatriptan, 2% with placebo). In participants with mild baseline pain, the NNTs were 8.5 and 6.0 for the 50 mg and 100 mg doses, respectively (about 25% to 30% responders with sumatriptan, 14% with placebo). For headache relief at one hour, sumatriptan 25 mg, 50 mg, and 100 mg compared with placebo gave NNTs of 9.0, 7.5, and 6.8, respectively (about 28% responders with sumatriptan, 13% with placebo), and for headache relief at two hours sumatriptan 25, 50, 100, 200, and 300 mg gave NNTs of 4.2, 4.0, 3.5, 2.1, and 2.4, respectively, when compared with placebo (about 60% to 70% responders with sumatriptan, 30% with placebo). For sustained pain-free during the 24 hours postdose the NNTs for sumatriptan 50 mg and 100 mg in participants with moderate or severe baseline pain were 9.5 and 6.5, respectively (about 20% responders with sumatriptan, 8% with placebo), while in participants with mild baseline pain they were 5.5 and 4.5, respectively (about 30% responders with sumatriptan, 10% with placebo). The NNTs for sustained headache relief during 24 hours, treating with sumatriptan 50 mg and 100 mg were 6.0 and 5.2, respectively (about 35% responders with sumatriptan, 17% with placebo).

Data were available for the use of rescue medication, the relief of headache-associated symptoms, and the relief of functional disability. The number of participants requiring rescue medication after treating with placebo (about 40% to 60%) was approximately double that after treating with sumatriptan 25 mg, 50 mg, or 100 mg (about 20% to 30%). This relationship appeared to hold regardless of whether the headache was treated early during the mild pain phase or when more established. Reported headache-associated symptoms included nausea, vomiting, photophobia, and phonophobia; vomiting occurred too infrequently for reliable analysis. Sumatriptan 25 mg, 50 mg, and 100 mg compared with placebo gave NNTs of between 7 and 8 for relief of nausea at two hours, and between 4 and 8 for relief of photophobia and phonophobia. Approximately half of participants treated with sumatriptan achieved relief of these symptoms, compared with approximately one-third of those treated with placebo. Functional disability was relieved (i.e. reduced from moderate or severe at baseline to mild or none at two hours) in approximately 50% of participants treated with sumatriptan 25 mg and 50 mg, and 60% of participants treated with sumatriptan 100 mg, compared with 25% to 30% of participants treated with placebo. This gave NNTs for relief of functional disability of 5.9, 5.6, and 3.6 for sumatriptan 25 mg, 50 mg, and 100 mg, respectively, when compared with placebo.

Analysis of adverse events was compromised by the fact that some studies did not specify the time period over which data were collected, and some specified time periods different from the 24-hour period specified in our review protocol. Furthermore, studies allowed use of rescue medication for inadequate response

(usually after two hours), and many allowed a second dose of study medication for headache recurrence (or sometimes lack of efficacy), without specifying whether adverse event data continued to be collected from participants who had taken additional medication. With these caveats, we chose to pool as much data as possible. More participants experienced adverse events with sumatriptan than with placebo, and a dose response relationship was seen over the range 25 mg to 100 mg, with NNHs ranging from 'not statistically significant' to 5.2. For the most part adverse events were described as mild to moderate in intensity and self limiting. It was noteworthy that adverse events with placebo were reported by 7% of participants with mild baseline pain, but by 23% with moderate or severe baseline pain, and correspondingly more with active treatment.

Serious adverse events were uncommon, and only four were reported as related to the study drug: one after treating with sumatriptan 85 mg (heart palpitations), one after treating with sumatriptan 300 mg (chest tightness and pressure), one after treating with ibuprofen 400 mg (perforation of duodenal ulcer), and one after treating with two doses of rizatriptan 20 mg (micturition-associated syncope). Withdrawals due to adverse events were uncommon. In placebo-controlled studies, excluding those using doses of sumatriptan greater than 100 mg, the rate of adverse event withdrawal after treating with sumatriptan was equivalent to that after placebo. Doses of sumatriptan greater than 100 mg showed slightly increased rates of withdrawal due to adverse events. For the most part individual adverse events occurred significantly more often with sumatriptan ≥ 100 mg than with placebo. Sumatriptan at doses of 50 mg or less was significantly different from placebo only for malaise/fatigue/asthenia and paraesthesia/numbness.

Of the active comparators used in the included studies, only rizatriptan 5 mg and 10 mg, effervescent ASA 1000 mg, zolmitriptan 2.5 mg and 5 mg, eletriptan 40 mg and 80 mg, almotriptan 12.5 mg, paracetamol 1000 mg + MCP 10 mg, and ASA 900 mg + MCP 10 mg provided sufficient data to be analysed for a particular outcome. Rizatriptan 5 mg was superior to sumatriptan 25 mg for pain-free at two hours and headache relief at two hours, but there was no significant difference between the treatments for headache relief at one hour; neither of these doses is commonly used. There was no difference between rizatriptan 5 mg and sumatriptan 50 mg for any outcomes reported. Rizatriptan 10 mg was superior to sumatriptan 25 mg, 50 mg, and 100 mg for all reported outcomes, including pain-free at two hours and headache relief at one and two hours. Effervescent ASA 1000 mg was more effective than sumatriptan 50 mg for headache relief at one hour, but there was no difference between the treatments for pain-free at one or two hours, and sumatriptan 50 mg was significantly superior for headache relief at two hours. For zolmitriptan 2.5 mg and 5 mg compared with sumatriptan 50 mg, there was no significant difference for headache relief at either one or two hours, and for almotriptan 12.5 mg compared with sumatriptan 100 mg, there was no significant difference for pain-free at two hours or sustained pain-free during the 24 hours postdose. Eletriptan 40 mg and 80 mg were superior to sumatriptan 50 mg and 100 mg for most reported outcomes, including pain-free at two hours, and headache relief at one and two hours. However, there was no significant difference between sumatriptan 50 mg and eletriptan 40 mg for headache relief at one hour, or sumatriptan 100 mg and eletriptan 40 mg for pain-free at one hour. There was no significant difference between sumatriptan 100 mg and either paracetamol + MCP, or ASA + MCP for headache relief at two hours. Sumatriptan 100 mg was, however, significantly superior to ASA + MCP for pain-free at two hours. For the majority of adverse events there was no significant difference between sumatriptan and any active comparator.

It should be noted that there were a very large number of analyses, with no correction for multiple comparisons, as is common with Cochrane reviews. The standard of statistical significance was a probability of a result occurring by chance of less than 5%, or 1 in 20. It is likely that many of the significant results obtained would not survive correction for multiple comparisons.

Overall completeness and applicability of evidence

Included participants suffered from migraine in accordance with IHS criteria (even if not specifically referenced in a few cases), with the majority suffering around one to six attacks per month and with a history of attacks for at least six months, and usually one year. In the majority of studies treated attacks had to be established, with moderate or severe pain intensity, before medication could be taken. The use of prophylactic medication during the study period was variable, with some studies requiring participants to discontinue any prophylactic medication at least two weeks before receiving study medication, while others allowed stable prophylactic medications, and others failed to comment at all. Nine studies excluded participants if they had previously taken sumatriptan, while four studies required participants to have experience of sumatriptan to be eligible for inclusion. Overall there did not appear to be a particular bias towards a certain type of migraine patient, but many studies recruited participants through headache clinics, which may have selected for those with more severe or hard-to-treat pain. Individuals were carefully screened before study entry, and those with certain conditions, particularly cardio- or cerebrovascular disease, were excluded from the studies. Other exclusions included pregnant or lactating women, individuals with hepatic disease or who regularly experience vomiting, and individuals who suffer from frequent non-migraine headaches or basilar, ophthalmic, or hemiplegic migraine. This may mean that the study population is not a reflection of a less carefully screened general population who may use sumatriptan.

While most studies reported IHS-preferred outcomes, they did not all report all the outcomes of interest for this review so that numbers of participants in any comparison were usually smaller than numbers treated.

Single-dose studies provide only limited information about adverse events, and individual studies are generally underpowered to assess harm, but pooling adverse event data from similar studies may allow more robust estimates for short-term use. In these studies the number of participants who experienced any adverse event was slightly increased with sumatriptan compared to placebo. However it is important to remember that in many studies rescue medication, or a second dose of study medication, was permitted if study medication failed to provide adequate relief, or in the event of recurrence, and this may disproportionately increase rates of adverse events in the placebo group. Some studies in this review reported data for individual adverse events only if they occurred at a specified rate, which differed across studies (> 1% to ≥ 5%), and inevitably means that some events occurring at lower frequencies were not reported in some studies.

Twenty studies allowed participants to treat a migraine attack during the mild pain phase. Despite this option to treat early, the majority of participants reported moderate or severe baseline pain intensity, and only six provided efficacy data for sumatriptan versus any comparator in participants with mild baseline pain intensity. In clinical practice many people treat their headache during this mild pain phase, and there is also some evidence that treating attacks in the early stages is beneficial (Gendolla 2008; Pascual 2002), which is supported by the data presented here. More studies reporting consistently on early treatment and different dosing strategies are needed to inform the best clinical use of oral sumatriptan.

The vast majority of included studies were industry-sponsored and are likely to have used GlaxoSmithKline-branded formulations of sumatriptan. Increasingly, migraine sufferers use generic formulations of sumatriptan (91% in the UK), and no clinical trials specifically using generic sumatriptan were found for inclusion in this review.

Quality of the evidence

The majority of included studies were of good methodological quality, with only 11/61 deemed to be of low quality (scoring 2 of 5 using the Oxford Quality Scale). However, 40 studies did not adequately describe random sequence generation, 47 studies did not provide information about allocation concealment, and 28 studies did not provide details on the method of blinding. In a number of studies withdrawals and dropouts were not reported adequately by treatment group, and for some outcomes reported denominators differed from the intention-to-treat (ITT) population, presumably because some participants failed to record data at that point. Wherever an adequate explanation was not given we have used the ITT denominator if it gave a more conservative estimate; in general, the number of missing participants was not sufficient to significantly alter the results. Nineteen studies had at least 200 participants in each treatment arm, a further 36 had between 50 and 200 in one or more treatment arms (the placebo arm was often smallest with other treatment arms having over 200 participants), and six had fewer than 50 participants in all treatment arms. Overall methodological quality of the included studies was good, and treatment group sizes were sufficiently big to avoid major bias in the results for efficacy.

While most studies used patient diaries and reported some information about adverse events, the outcomes were not always our preferred ones, and the time over which data were collected was frequently not explicit. It is likely that data continued to be collected after intake of rescue medication or a second dose of study medication, so that total dose over the period assessed is uncertain.

Potential biases in the review process

We identified a large amount of data in comparisons with placebo, particularly for the 50 mg and 100 mg doses. Over 4000 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) for the 50 mg dose (Moore 2008). This equates to 10 studies with over 400 participants in sumatriptan 50 mg and placebo treatment arms. Similarly, over 2000 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), equivalent to 10 trials with over 200 sumatriptan 50 mg and placebo-treated participants in each. It is unlikely that such a large amount of unidentified data exists, so publication bias is not a concern.

The methods of review were such as to minimise bias due to the review process itself, but use of data from both phases of cross-over studies and from studies reporting combined data from several attacks may introduce unknown biases. For cross-over studies a 48-hour period between qualifying attacks should limit potential for carryover effects, and for multiple attacks there is some evidence of consistency of response (in terms of proportion of participants achieving the outcome) for aspirin in migraine (Kirthi 2010) and within some studies in this review (Bussone 2000; Gallagher 2000; GL/MIG/001/92; GL/MIG/001A/92; GL/MIG/002; GL/MIG/002A; GL/MIG/009; Gruffyd-Jones 2001; Myllyla 1998; Pfaffenrath 1998; Sandrini 2002; Tfelt-Hansen 1995; Thomson 1992).

We specified that a minimum of 200 participants in at least two studies were required before carrying out any pooled analysis, but ideally we would need at least 200 participants in each treatment arm where there is an event rate of 50% to be reasonably confident in the size of an effect (Moore 2010). The magnitude of effect for outcomes with fewer participants and/or lower event rates should be interpreted with caution.

Agreements and disagreements with other studies or reviews

The earlier Cochrane review of sumatriptan for acute migraine (McCrory 2003) reported results for sumatriptan 100 mg, 50 mg, and 25 mg versus placebo. These results were broadly consistent with those reported here, with the additional data included in this review resulting in much tighter confidence intervals. The new data did, however, change the estimated effects of sumatriptan 50 mg versus placebo for pain-free at two hours (which appears to have been overestimated previously) and sumatriptan 100 mg versus placebo for incidence of adverse events (which appears to have been underestimated previously).

Similarly, the results presented here were also largely consistent with those presented in a previous review of triptan use in acute migraine (Gawel 2001) which included data from 13 studies comparing oral sumatriptan with placebo, of which all but two (Centonze 1995; Rederich 1995) were included in our review. Again additional data included in our review resulted in a slightly reduced estimate of efficacy for both the 50 mg and 100 mg doses and tighter confidence intervals.

Ferrari and colleagues (Ferrari 2001) reviewed all triptan studies available up to 2001. They used the approach of presenting the absolute percentage benefiting, and the absolute benefit increase (active minus placebo). Results in that analysis are in line with those presented here.

Oldman 2002 reviewed all pharmacological treatments for acute migraine, including 15 studies involving oral sumatriptan, all of which are included here (two unpublished studies included have subsequently been published as Goadsby 2000 and Sandrini 2002 and are included in this review). Again, the results are in good agreement with those presented in our review: NNTs for headache relief at two hours with both sumatriptan 50 mg and 100 mg were

very similar, while NNTs for headache relief at one hour with the two doses of sumatriptan were slightly decreased with the additional data included in this review.

AUTHORS' CONCLUSIONS

Implications for practice

Oral sumatriptan is an effective treatment for the relief of headache pain, other symptoms associated with migraine, and functional disability, with single doses of 25 mg or more providing clinically useful levels of relief in some people. Higher doses are effective in more individuals, but at the expense of greater numbers of adverse events. Most events were described as mild and of short duration. The number of participants experiencing headache relief by one hour after administration is low, and the number pain-free by one hour is not clinically useful. Treating attacks early, during the mild pain phase, results in significantly greater efficacy, but does not significantly change the incidence of adverse events.

These data support the general guideline advice to use 50 mg as the starting dose, with increases to 100 mg if necessary and tolerated. Some experienced patients may find that a 25 mg dose is sufficient.

Implications for research

A useful line of research would be to investigate whether sumatriptan is a useful second-line treatment for individuals who fail to get an adequate response with simple analgesics, such as ibuprofen or aspirin.

There is an abundance of data on the efficacy of sumatriptan in terms of pain relief, but in general, reporting of long-term (sustained to 24 hours or 48 hours) and secondary outcomes such as relief of headache-associated symptoms, functional disability, and adverse events is less good. Future studies should address sustained outcomes and consistently report relief of associated symptoms, functional disability and adverse events using standard definitions.

More studies are needed to establish whether treating pain early, while still mild, gives better short-term (two-hour) and long-term (sustained to 24 hours or 48 hours) outcomes, and better patient satisfaction.

ACKNOWLEDGEMENTS

GlaxoSmithKline provided additional information relating to methods in five of the unpublished studies included in this review. Pfizer provided a clinical trial report for eletriptan protocol 160-104, the sixth unpublished study included in this review.

We would like to acknowledge the helpful comments and editorial expertise of Timothy Steiner, Douglas McCory, and Rebecca Gray, and those who contributed to the various stages of peer review.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

160-104

Methods	Multicentre, randomised, double-blind, double-dummy, placebo-controlled, parallel-group. Single dose to treat each of up to 3 separate attacks. Medication administered when migraine headache pain was of moderate or severe intensity Assessments at 0.5, 1, 2, and 4 hours after dosing Second dose (either same as first dose of study medication or a double-blind placebo) available after 2 hours for inadequate response, or for recurrence of headache within 24 hours of initial dosing Alternative rescue medication available 2 hours after second dose if appropriate

160-104 *(Continued)*

Participants	Aged 18 years or over and suffering at least 1 acute attack of migraine, with or without aura (IHS 1988), every 6 weeks Participants excluded if ever taken sumatriptan before (any formulation) or oral eletriptan No prescription analgesic or antiemetic within 6 hours prior to study treatment. No sumatriptan, ergotamine, or ergotamine-like agent within previous 48 hours. N = 818 (treated first attack) M 150, F 668 (82%) Mean age 35 years Without aura 86%
Interventions	Numbers of participants treating first attack Sumatriptan 25 mg, n = 180 Sumatriptan 50 mg, n = 181 Eletriptan 40 mg, n = 184 Eletriptan 80 mg, n = 180 Placebo, n = 93
Outcomes	Headache relief (at 1 and 2 h) Pain-free (at 2 h) Relief of nausea, photophobia, and phonophobia at 2 hours Relief of functional disability at 2 hours Adverse events Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5. Pharmaceutical industry support: Pfizer

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated pseudo-random code using the method of random permuted blocks
Allocation concealment (selection bias)	Low risk	Next consecutive number corresponding to study drug in blister card
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-dummy
Study size	Unclear risk	Treatment groups 50 to 200 participants

Banerjee 1992

Methods	Multicentre, randomised, double-blind, placebo-controlled, parallel-group. Single dose to treat each of up to 3 separate attacks. Medication administered as soon as migraine attack with aura recognised Assessments at 2 and 6 h after dosing Rescue medication available after 2 h for inadequate symptom relief At least a 48-h interval between treated attacks
Participants	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with aura. At least 1-year history of migraine (untreated severity ≥ moderate) with an average of 1 to 6 attacks per month. Migraine prophylaxis discontinued at least 2 weeks prior to entering the study N = 94 (71 for efficacy) M 14, F 80 (85%) Mean age 35 years Proportion with/without aura not reported
Interventions	Sumatriptan (dispersible) 200 mg, n = 37 (34 for efficacy) Placebo, n = 39 (37 for efficacy)
Outcomes	Headache relief (at 2 h) Pain-free (at 2 h) Persistence of nausea, vomiting, and photophobia at 2 h Use of rescue medication Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB1, W1. Total = 3. Pharmaceutical industry support: Glaxo Group Research Ltd.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Study size	High risk	Treatment groups < 50 participants

Brandes 2007

Methods	Multicentre, randomised, double-blind, placebo-controlled, parallel-group. Single dose to treat single attack. Medication administered when migraine headache pain was of moderate or severe intensity Assessment at 0.5, 1, 1.5, and 2 h and then hourly from 2 to 24 h after dosing Rescue medication available after 2 h, excepting ergot-containing medications, serotonin agonists, or NSAID-containing products 2 replicate studies: Study 1 and 2
Participants	Aged 18 to 65 years, meeting IHS criteria for migraine (2004) with or without aura. At least 6-month history of migraine (untreated severity ≥ moderate) with an average of 2 to 6 attacks per month. Participants excluded if experienced more than 6 migraine attacks per month in the 2 months before screening, or had chronic daily headache (≥ 15 days per month of non-migraine headaches) during the 3 months before screening No ergotamine use within 3 months, no monoamine oxidase inhibitor use within 2 weeks, and no St. John's wort use within 4 weeks of taking study medication. No regular NSAID use. No NSAID, opiate, or ergotamine use within 24 h, and no other analgesic or antiemetic use within 6 h of taking study medication. Study 1 N = 1677 (1461 for efficacy) M 187, F 1254 (87%) Mean age 40 years Without aura 74% Study 2 N = 1736 (1495 for efficacy) M 153, F 1317 (90%) Mean age 40 years Without aura 77%
Interventions	Study 1 Sumatriptan 85 mg, n = 415 (365 for efficacy) Naproxen 500 mg, n = 419 (361 for efficacy) Sumatriptan 85 mg + naproxen 500 mg, n = 422 (370 for efficacy) Placebo, n = 421 (365 for efficacy) Study 2 Sumatriptan 85 mg, n = 434 (370 for efficacy) Naproxen 500 mg, n = 434 (371 for efficacy) Sumatriptan 85 mg + naproxen 500 mg, n = 433 (367 for efficacy) Placebo, n = 435 (387 for efficacy)

Brandes 2007 *(Continued)*

Outcomes	Headache relief (at 2 h) Pain-free (at 2 h) 24 h sustained headache relief 24 h sustained pain-free Improvement in nausea, photophobia, and phonophobia at 2 h Improvement in functional disability at 2 h (from Landy 2007 (secondary reference for this study)) Use of rescue medication Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB1, W1. Total = 3. Pharmaceutical industry support: GlaxoSmithKline and Pozen Inc.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Study size	Low risk	Treatment groups > 200 participants

Bussone 2000

Methods	Multicentre, randomised, double-blind, cross-over. Single dose to treat each of up to 12 consecutive attacks. Medication administered when migraine headache pain was of moderate or severe intensity Assessments at 2 and 4 h after dosing Rescue medication available after 4 h for inadequate relief Second dose of study medication available for recurrence between 4 and 24 h At least 24 h between separate attacks, otherwise defined as recurrence
Participants	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity ≥ moderate) with an average of 1 to 6 attacks per month. Ergotamine and migraine prophylaxis discontinued before taking study medication N = 233

Bussone 2000 *(Continued)*

	M 49, F 184 (79%) Mean age 37 years Proportion with/without aura not reported
Interventions	Sumatriptan 50 mg, n = 156 Placebo, n = 56
Outcomes	Headache relief (at 2 h) Persistence of functional disability at 2 h Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB1, W0. Total = 2. Pharmaceutical industry support: Glaxo Wellcome

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Study size	Unclear risk	Treatment groups 50 to 200 participants

Carpay 2004

Methods	Multicentre, randomised, double-blind, placebo-controlled, parallel-group. Single dose to treat single attack. Medication administered within 1 h of the onset of mild pain while pain was still mild Assessments at 0.5, 0.75, 1, 2, and 24 h after dosing Second dose of study medication available to treat recurrence in individuals experiencing pain-free results at 2 h Rescue medication (excluding ergot-containing medication or triptans) available after 2 h for inadequate relief or recurrence (in individuals not wanting a second dose of study medication)
Participants	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity ≥ moderate), typically preceded by a mild-pain phase, and with an average of 1 to 6 attacks per month. Participants excluded if they had more than 6 migraines per month during either of the 2 months before screening.

Carpay 2004 *(Continued)*

	Migraine prophylactic medication containing ergotamine, ergotamine-derivatives, or methysergide, and use of monoamine oxidase inhibitors was discontinued 2 weeks before the study. N = 481 (444 for efficacy) M 74, F 358 (83%) Mean age 41 years Without aura 71%
Interventions	Sumatriptan (fast disintegrating) 50 mg, n = 141 Sumatriptan (fast disintegrating) 100 mg, n = 148 Placebo, n = 155
Outcomes	Pain-free (at 1 and 2 h) 24 h sustained pain-free Improvement in nausea, photophobia, and phonophobia at 2 h Improvement in functional disability at 2 h (from Barbanti 2004 (secondary reference for this study)) Adverse events
Notes	Oxford Quality Score: R1, DB1, W0. Total = 2. Pharmaceutical industry support: GlaxoSmithKline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Study size	Unclear risk	Treatment groups 50 to 200 participants

Cutler 1995

Methods	Multicentre, randomised, double-blind, placebo-controlled, parallel-group. Single dose to treat single attack. Medication administered when migraine headache pain was of moderate or severe intensity. Assessment at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, and 4 h after dosing. Rescue medication (acetaminophen) was available after 2 h if pain had not improved relative to pre-dose levels. After 4 h, rescue medication other than acetaminophen was allowed if pain had still not improved.

Cutler 1995 *(Continued)*

Participants	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity ≥ moderate) with an average of 1 to 6 attacks per month. Migraine prophylaxis not allowed during 2-week period preceding treatment. No opioid-containing agents or ergotamine within 24 h, or simple analgesics within 6 h of taking study medication. N = 259 M 22, F 237 (92%) Mean age 39 years Proportion with/without aura not reported
Interventions	Sumatriptan 25 mg, n = 66 Sumatriptan 50 mg, n = 62 Sumatriptan 100 mg, n = 66 Placebo, n = 65
Outcomes	Headache relief (at 2 h) Pain-free (at 2 h) Improvement in nausea and photophobia at 2 h Improvement in functional disability at 2 h Adverse events
Notes	Oxford Quality Score: R1, DB1, W0. Total = 2. Pharmaceutical industry support: Glaxo Research Institute

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Study size	Unclear risk	Treatment groups 50 to 200 participants

Dahlof 1991

Methods	Multicentre, randomised, double-blind, placebo-controlled, parallel-group. Single dose to treat each of 3 consecutive attacks. Medication was administered at the earliest sign of an attack Assessment at 2 h after dosing

Dahlof 1991 *(Continued)*

	Rescue medication (provided it did not contain ergotamine) was available after 2 h for inadequate symptom relief Minimum of 48 h between treated attacks
Participants	Aged 18 to 60 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity ≥ moderate) with an average of 1 to 6 attacks per month. Use of migraine prophylactic therapy was stopped at least 2 weeks before receipt of study medication N = 1130 (984 with moderate or severe baseline pain intensity) M 187, F 943 (83%) Mean age 40 years Without aura 33%
Interventions	Sumatriptan 100 mg, n = 305 (275 with moderate or severe baseline pain intensity) Sumatriptan 200 mg, n = 283 (255 with moderate or severe baseline pain intensity) Sumatriptan 300 mg, n = 299 (271 with moderate or severe baseline pain intensity) Placebo, n = 205 (182 with moderate or severe baseline pain intensity)
Outcomes	Headache relief (at 2 h) Improvement in nausea, vomiting, and photophobia at 2 h Patients' opinion of treatment Use of rescue medication Consistency of response Adverse events Withdrawals due to adverse events
Notes	Oxford Quality Score: R1, DB1, W0. Total = 2. Pharmaceutical industry support: Glaxo Group Research Ltd.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Study size	Low risk	Treatment groups > 200 participants

Dahlof 2009

Methods	Multicentre, randomised, double-blind, placebo-controlled, parallel-group. Single dose to treat single attack. Medication administered when migraine headache pain was of moderate or severe intensity Assessments at 0.5, 1, 2, 4, and 24 h after dosing Rescue medication available after 2 h
Participants	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity ≥ moderate) with an average of 1 to 6 attacks per month. Participants excluded if they treated non-migrainous headaches with analgesia for more than 10 days per month over the 6 months before screening No ergotamine, ergot-derivatives, or triptans within 24 h, or any analgesics within 6 h of taking study medication N = 667 (541 for efficacy) M 85, F 456 (84%) Mean age 40 years Without aura 74%
Interventions	Sumatriptan 50 mg, n = 136 Tonabersat 20 mg, n = 134 Tonabersat 40 mg, n = 137 Placebo, n = 134
Outcomes	Headache relief (at 1 and 2 h) Pain-free (at 1 and 2 h) Use of rescue medication Adverse events Withdrawals
Notes	Oxford Quality Score: R2, DB1, W1. Total = 4. Pharmaceutical industry support: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list
Allocation concealment (selection bias)	Low risk	Remote allocation, sealed envelopes
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported

Dahlof 2009 *(Continued)*

Study size	Unclear risk	Treatment groups 50 to 200 participants

Diener 2004a

Methods	Multicentre, randomised, double-blind, double-dummy, placebo-controlled, parallel-group. Single dose to treat single attack. Medication administered when migraine headache pain was of moderate or severe intensity Assessments at 0.5, 1, 1.5, 2, and 24 h after dosing Participants were encouraged to wait until 2 h after dosing before taking rescue medication if they experienced inadequate symptomatic relief, although it was available at any time during the study
Participants	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 6-month history of migraine (untreated severity ≥ moderate) with an average of 1 to 6 attacks per month. At the time of treatment participants had to be without aura with each of the following associated symptoms was present: nausea, photophobia, and phonophobia Participants must have been free from any previous migraine for at least 24 h N = 435 (433 for efficacy) M 66, F 367 (85%) Mean age 43 years Without aura 79%
Interventions	Sumatriptan 50 mg, n = 135 Effervescent acetylsalicylic acid 1000 mg, n = 147 (146 for efficacy) Placebo, n = 153 (152 for efficacy)
Outcomes	Headache relief (at 1 and 2 h) Pain-free (at 1 and 2 h) Improvement in nausea, photophobia, and phonophobia at 2 h Patients' opinion of treatment Use of rescue medication Adverse events
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5. Pharmaceutical industry support: Bayer AG

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list

Diener 2004a *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-dummy technique
Study size	Unclear risk	Treatment groups 50 to 200 participants

Diener 2004b

Methods	Multicentre, randomised, double-blind, double-dummy, placebo-controlled, cross-over. Single dose to treat each of 3 successive attacks. Medication administered when migraine headache pain was of moderate or severe intensity Assessments at 0.5, 1, 1.5, and 2 h after dosing Participants were encouraged to wait until 2 h after dosing before taking rescue medication if they experienced inadequate symptomatic relief, although it was available at any time during the study Minimum of 48 h between consecutive study treatments
Participants	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity ≥ moderate) with an average of 1 to 6 attacks per month. Participants were excluded if they experienced any other type of headache, including tension-type headache N = 313 (312 for efficacy) M 59, F 253 (81%) Mean age 38 years Without aura 79%
Interventions	Sumatriptan 50 mg, n = 226 Ibuprofen 400 mg, n = 212 Effervescent acetylsalicylic acid 1000 mg, n = 222 Placebo, n = 222
Outcomes	Headache relief (at 1 and 2 h) Pain-free (at 1 and 2 h) Improvement in nausea, vomiting, photophobia, and phonophobia at 2 h Patients' opinion of treatment Use of rescue medication Adverse events
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4. Pharmaceutical industry support: Bayer AG

Diener 2004b *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-dummy technique
Study size	Low risk	Treatment groups > 200 participants

DKSMSG 1999

Methods	Multicentre, randomised, double-blind, double-dummy, within-patient cross-over. Single dose to treat each of 4 consecutive attacks. Medication administered at the first sign of migraine pain Assessments at 0.3, 0.7, 1, 1.5, 2, 3, 4, 6, and 8 h after dosing Paracetamol available as rescue medication after 2 h for inadequate symptom relief Each treated attack separated by at least a 48-h period free of acute headache medication and migraine symptoms
Participants	Aged 18 years or over, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity ≥ moderate) with an average of 2 to 6 attacks per month. N = 156 (144 received at least 1 treatment, 115 completed treatment for all 4 attacks) M 37, F 119 (76%) Mean age 33 years Proportion with/without aura not reported
Interventions	Sumatriptan 100 mg, n = 130 Diclofenac-potassium 50 mg, n = 131 Diclofenac-potassium 100 mg, n = 122 Placebo, n = 131
Outcomes	Improvement in nausea, vomiting, photophobia, and phonophobia at 2 h Use of rescue medication Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4.

DKSMSG 1999 *(Continued)*

	Pharmaceutical industry support: Novartis Pharma

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-dummy technique
Study size	Unclear risk	Treatment groups 50 to 200 participants

Dodick 2002

Methods	Multicentre, randomised, double-blind, placebo-controlled, parallel-group. Single dose to treat single attack. Medication administered when migraine headache pain was of moderate or severe intensity Assessments over 24 h following dosing and specifically at 2 h postdose Second dose of study medication available to treat recurrence within 24 h Rescue medication (excluding ergot alkaloids and 5-$HT_{1B/1D}$ agonists) was available if moderate-to-severe migraine pain persisted 2 h after initial dosing Of the 3 studies reported, only protocol CL13 is relevant
Participants	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity ≥ moderate) with an average of 1 to 6 attacks per month, each separated by at least a 24-h headache-free period. Participants were excluded if they had a history of migraine with prolonged aura or if they experienced more than 6 headaches per month. No migraine medications (e.g. analgesics, NSAIDS, 5-$HT_{1B/1D}$ receptor agonists, or dopamine agonists) for 2 days prior to intake of study medication. No antipsychotic or antidepressant medication within the 3 months preceding study enrolment, or any investigational drug within 1 month of study enrolment. Protocol CL13 N = 475 M 69, F 406 (85%) Mean age 43 years Without aura 79%
Interventions	Protocol CL13 Sumatriptan 100 mg, n = 193

Dodick 2002 *(Continued)*

	Almotriptan 12.5 mg, n = 183
	Placebo, n = 99
Outcomes	Pain-free (at 2 h)
	24-h sustained pain-free
	Use of rescue medication
Notes	Oxford Quality Score: R1, DB1, W0. Total = 2.
	Pharmaceutical industry support: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Study size	Unclear risk	Treatment groups 50 to 200 participants

Dowson 2002

Methods	Multicentre, randomised, double-blind, placebo-controlled, parallel-group. Single dose to treat single attack.
	Medication administered when migraine headache pain was of moderate or severe intensity
	Assessments at 1, 2, and 24 h after dosing
	Second dose of study medication available to treat recurrence within 24 h
	Rescue medication (excluding ergot-derivatives) available if migraine pain did not disappear or become mild within 2 h of treatment
Participants	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity ≥ moderate) with an average of 1 to 6 attacks per month, each separated by at least a 24-h headache-free period.
	Participants were excluded if they had a history of migraine with prolonged aura or if they needed symptomatic medication for migraine in the 2 days before taking study medication.
	No investigational drug within 1 month of study treatment. No monoamine oxidase inhibitors, lithium, selective serotonin reuptake inhibitors, ergots or derivatives, or methysergide in the 2 weeks prior to study medication.
	N = 668
	M 101, F 567 (85%)
	Mean age 42 years

Dowson 2002 *(Continued)*

	Without aura 78%
Interventions	Sumatriptan 100 mg, n = 194 Almotriptan 12.5 mg, n = 184 Almotriptan 25 mg, n = 191 Placebo, n = 99
Outcomes	Headache relief (at 1 and 2 h) Pain-free (at 1 and 2 h) 24-h sustained pain-free (from Dowson 2004 (secondary reference for this study)) Improvement in nausea, vomiting, photophobia, and phonophobia at 2 h Use of rescue medication Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB1, W1. Total = 3. Pharmaceutical industry support: Almirall SA

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Study size	Unclear risk	Treatment groups 50 to 200 participants

Ensink 1991

Methods	Multicentre, randomised, double-blind, placebo-controlled, parallel-group. Single dose to treat single attack. Medication administered as soon as possible after onset of headache Assessments at 2, 4, and 24 h after dosing Second dose of study medication available after 2 h if headache persisted. Alternative rescue medication available 2 h after the second dose of study medication if their headache had not resolved. Third dose of study medication available to treat headache recurrence within 24 h
Participants	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity ≥ moderate) with an average of 1 to 6 attacks per month.

Ensink 1991 *(Continued)*

	No prophylactic medication within 2 weeks of the start of the study
	N = 233 (232 for efficacy, 209 with moderate or severe baseline pain intensity)
	M 34, F 198 (85%)
	Mean age 41 years
	Without aura 67%
Interventions	Sumatriptan 100 mg, n = 148 (131 with moderate or severe baseline pain intensity)
	Placebo, n = 84 (78 with moderate or severe baseline pain intensity)
Outcomes	Headache relief (at 2 h)
	Pain-free (at 2 h)
	Persistence of nausea and vomiting at 2 h
	Improvement in photo/phonophobia at 2 h
	Improvement in any headache associated symptoms at 2 h
	Patients' opinion of treatment
	Use of rescue medication
	Adverse events
Notes	Oxford Quality Score: R1, DB1, W0. Total = 2.
	Pharmaceutical industry support: Glaxo Group Research Ltd.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Study size	Unclear risk	Treatment groups 50 to 200 participants

Freitag 2001

Methods	Multicentre, randomised, double-blind, double-dummy, parallel-group. Multiple doses to treat single attack, after initial dose participants were allowed additional doses on a hourly basis for the next 3 h (see interventions for precise dosing schedule).
	Medication administered at the first signs or symptoms of acute migraine attack
	Assessments at 0.5, 1, 2, 3, 4, and 24 h after initial dosing

Freitag 2001 *(Continued)*

	Participants asked to refrain from taking rescue medications until at least 2 h after initial dosing
Participants	Aged 18 or over, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity ≥ moderate) with an average of 2 to 8 attacks per month. Participants were excluded if their migraines were accompanied by vomiting more than 20% of the time or required bed rest for at least half of their attacks Prophylactic migraine medications were continued if the dose had been stable prior to study enrolment No monoamine oxidase inhibitors or methysergide within 2 weeks of study enrolment N = 128 (126 for efficacy) M 14, F 112 (89%) Mean age 42 years Without aura 90%
Interventions	Sumatriptan 25 mg (+ additional dose of 25 mg at 2 h), n = 61 Isometheptene combination (isometheptene mucate + dichloralphenazone + acetaminophen) 2 doses (+ additional single doses at 1, 2 and 3 h), n = 65
Outcomes	Headache relief (at 1 and 2 h) Improvement in nausea, photophobia, and phonophobia at 1 h Improvement in functional disability at 1 h Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4. Pharmaceutical industry support: Carnrick Laboratories

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-dummy technique
Study size	Unclear risk	Treatment groups 50 to 200 participants

Gallagher 2000

Methods	Multicentre, randomised, double-blind, parallel-group. Single dose to treat each of at least 2 separate attacks (up to 6).

Gallagher 2000 *(Continued)*

	Medication administered when migraine headache pain was of moderate or severe intensity Assessments at 1, 2, 4, and 24 h after dosing Second dose of study medication available to treat recurrence occurring 4 to 24 h after the initial dose Rescue medication (excluding acute antimigraine treatments such as sumatriptan, ergotamine, dihydroergotamine, and isometheptene) was available 2 h after the last dose of study medication to treat persistent headache
Participants	Aged 18 to 65, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity ≥ moderate). Participants were excluded if they had experienced non-migraine headache for 10 or more days per month over the previous 6 months No monoamine oxidase inhibitors, methysergide, methylergonovine, fenfluramine, or dexfenfluramine use during the study period. N = 1338 (1212 for efficacy) M 150, F 1062 (88%) Mean age 40 years Without aura 57%
Interventions	Sumatriptan 25 mg, n = 336 (306 for efficacy) Sumatriptan 50 mg, n = 338 (306 for efficacy) Zolmitriptan 2.5 mg, n = 327 (295 for efficacy) Zolmitriptan 5 mg, n = 337 (305 for efficacy)
Outcomes	Headache relief (at 1 and 2 h) 24-h sustained headache relief Improvement in nausea and photophobia Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB1, W1. Total = 3. Pharmaceutical industry support: Zeneca Inc.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported

Gallagher 2000 *(Continued)*

Study size	Low risk	Treatment groups > 200 participants

Geraud 2000

Methods	Multicentre, randomised, double-blind, double-dummy, placebo-controlled, parallel-group. Single dose to treat single attack. Medication administered when migraine headache pain was of moderate or severe intensity Assessments at 1, 2, 4, and 24 h after dosing Rescue medication was available after 2 h if migraine symptoms persisted. However ergot derivatives were not permitted until 12 h after study medication, and sumatriptan could not be used as a rescue medication.
Participants	Aged 18 to 65, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity ≥ moderate) with an average of 1 to 6 attacks per month. Participants were excluded if they had taken sumatriptan or zolmitriptan previously Participants were permitted to use medications such as β-blockers, calcium channel blockers (excluding flunarizine), clonidine, and valproic acid for migraine prophylaxis. However, they were excluded if they had received regular treatment during the month preceding the study with psychoactive drugs or drugs with a clinically important action at a 5-HT receptor. N = 1058 M 174, F 884 (84%) Mean age 38 years Without aura 73%
Interventions	Sumatriptan 100 mg, n = 504 Zolmitriptan 5 mg, n = 498 Placebo, n = 56
Outcomes	Headache relief (at 1 and 2 h) Pain-free (at 1 and 2 h) 24-h sustained headache relief Improvement in nausea, photophobia, and phonophobia at 2 h Improvement in functional disability at 2 h Use of rescue medication Adverse events
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4. Pharmaceutical industry support: Glaxo Wellcome

Risk of bias

Bias	Authors' judgement	Support for judgement

Geraud 2000 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-dummy technique
Study size	Unclear risk	Active treatment groups > 200 participants, placebo treatment group 56 participants

GL/MIG/001/92

Methods	Multicentre, randomised, double-blind, double-dummy, parallel-group. Single dose to treat each of up to 3 attacks. Assessments at 2 and 4 h after dosing Second dose of either sumatriptan (sumatriptan-treated group) or placebo (paracetamol/metoclopramide group) was available after 2 h if necessary Rescue medication (usual non-ergotamine containing migraine treatments) was available after 4 h if study medication had not provided adequate relief
Participants	Aged 20 to 65, at least 1-year history of migraine (diagnostic criteria equivalent to IHS 1988) with or without aura, and a frequency of at least 1 attack every 8 weeks Participants were excluded if they had taken sumatriptan previously No migraine prophylactic therapy or ergotamine-containing medications within 2 weeks before study treatment N = 607 (469 with moderate or severe baseline pain intensity) M 98, F 509 (84%) Mean age 39 years Proportion with/without aura not reported
Interventions	Sumatriptan 100 mg, n = 305 (242 with moderate or severe baseline pain intensity) Paracetamol 1000 mg + metoclopramide 10 mg, n = 302 (227 with moderate or severe baseline pain intensity)
Outcomes	Headache relief (at 2 h) Improvement in nausea, vomiting, and photo/phonophobia at 2 h Use of rescue medication Adverse events Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5.

GL/MIG/001/92 *(Continued)*

	Pharmaceutical industry support: Glaxo Group Research Ltd.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation code
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-dummy technique
Study size	Low risk	Treatment groups > 200 participants

GL/MIG/001A/92

Methods	Multicentre, randomised, double-blind, double-dummy, parallel-group. Single dose to treat each of up to 3 attacks. Assessments at 2 and 4 h after dosing Rescue medication (usual non-ergotamine containing migraine treatments) was available after 4 h if study medication had not provided adequate relief
Participants	Aged 20 to 65, at least 1-year history of migraine (diagnostic criteria equivalent to IHS 1988) with or without aura, and a frequency of at least 1 attack every 8 weeks Participants were excluded if they had taken sumatriptan previously No migraine prophylactic therapy or ergotamine-containing medications within 2 weeks before study treatment N = 721 (566 with moderate or severe baseline pain intensity) M 124, F 597 (83%) Mean age 40 years Proportion with/without aura not reported
Interventions	Sumatriptan 100 mg, n = 348 (272 with moderate or severe baseline pain intensity) Paracetamol 1000 mg + metoclopramide 10 mg, n = 373 (294 with moderate or severe baseline pain intensity)
Outcomes	Headache relief (at 2 h) Improvement in photo/phonophobia at 2 h Use of rescue medication Adverse events Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5.

GL/MIG/001A/92 *(Continued)*

Pharmaceutical industry support: Glaxo Group Research Ltd.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation code
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-dummy technique
Study size	Low risk	Treatment groups > 200 participants

GL/MIG/002

Methods	Multicentre, randomised, double-blind, parallel-group. Single dose to treat each of up to 3 attacks. Medication administered at the onset of migraine Assessments at 2 and 4 h after dosing Second dose of either sumatriptan (sumatriptan-treated group) or placebo (Migraleve group) was available for inadequate relief after 2 h Rescue medication was available after 4 h if study medication had not provided adequate relief
Participants	Aged 18 to 65, at least 1-year history of migraine (diagnostic criteria equivalent to IHS 1988) with or without aura (untreated severity ≥ moderate), and a frequency of at least 1 attack every 8 weeks Participants were excluded if they had taken sumatriptan previously, or were receiving prophylactic therapy for migraine, constant analgesic therapy for other diseases, or antiemetics (regularly or irregularly) No ergotamine-containing medications within 2 weeks before study treatment N = 752 (of which 709 treated attack 1, and 532 had ≥ moderate baseline pain intensity) M 112, F 640 (85%) Mean age 41 years Proportion with/without aura not reported
Interventions	Sumatriptan 100 mg, n = 374 (262 with moderate or severe baseline pain intensity) Migraleve (buclizine hydrochloride 12.5 mg + paracetamol 1000 mg + codeine phosphate 16 mg), n = 378 (275 with moderate or severe baseline pain intensity)
Outcomes	Headache relief (at 2 h) Improvement in nausea, vomiting, and photo/phonophobia at 2 h Use of rescue medication Adverse events

GL/MIG/002 *(Continued)*

	Withdrawals
Notes	Oxford Quality Score: R1, DB1, W1. Total = 3. Pharmaceutical industry support: Glaxo Group Research Ltd.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Study size	Low risk	Treatment groups > 200 participants

GL/MIG/002A

Methods	Multicentre, randomised, double-blind, parallel-group. Single dose to treat each of up to 3 attacks. Medication administered at the onset of migraine Assessments at 2 and 4 h after dosing Rescue medication was available after 4 h if study medication had not provided adequate relief
Participants	Aged 18 to 65, at least 1 year history of migraine (diagnostic criteria equivalent to IHS 1988) with or without aura (untreated severity ≥ moderate), and a frequency of at least 1 attack every 8 weeks Participants were excluded if they had taken sumatriptan previously, or were receiving prophylactic therapy for migraine, constant analgesic therapy for other diseases, or antiemetics (regularly or irregularly) No ergotamine-containing medications within 2 weeks before study treatment N = 674 (of which 617 treated attack 1, and 518 had ≥ moderate baseline pain intensity) M 112, F 562 (83%) Mean age 41 years Proportion with/without aura not reported
Interventions	Sumatriptan 100 mg, n = 342 (261 with moderate or severe baseline pain intensity) Migraleve (buclizine hydrochloride 12.5 mg + paracetamol 1000 mg + codeine phosphate 16 mg), n = 332 (257 with moderate or severe baseline pain intensity)
Outcomes	Improvement in photo/phonophobia at 2 h Use of rescue medication Adverse events

GL/MIG/002A *(Continued)*

	Withdrawals
Notes	Oxford Quality Score: R1, DB1, W1. Total = 3. Pharmaceutical industry support: Glaxo Group Research Ltd.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Study size	Low risk	Treatment groups > 200 participants

GL/MIG/009

Methods	Multicentre, randomised, double-blind, parallel-group. Single dose to treat each of up to 3 attacks. Medication administered at the onset of migraine Assessments at 1, 2, and 4 h after dosing Second dose of study medication was available for inadequate relief after 2 h Alternative rescue medication was available after 4 h if study medication had not provided adequate relief
Participants	Aged 18 to 65, at least 1-year history of migraine (diagnostic criteria equivalent to IHS 1988) with or without aura (untreated severity ≥ moderate), and a frequency of at least 1 attack every 4 weeks with at least 24 hours of freedom from headache between attacks No migraine prophylactic therapy, or ergotamine-containing medications within 2 weeks before study treatment N = 513 (of which 468 treated attack 1, and 407 had ≥ moderate baseline pain intensity) M 83, F 430 (84%) Mean age 40 years Proportion with/without aura not reported
Interventions	Sumatriptan 100 mg, n = 255 (203 with moderate or severe baseline pain intensity) Migril (ergotamine tartrate 2 mg + cyclizine hydrochloride 50 mg + caffeine hydrate 100 mg), n = 258 (204 with moderate or severe baseline pain intensity)
Outcomes	Headache relief (at 1 and 2 h) Pain-free (at 1 and 2 h) Improvement in nausea, vomiting, and photo/phonophobia at 2 h

GL/MIG/009 *(Continued)*

	Use of rescue medication
	Adverse events
	Withdrawals
Notes	Oxford Quality Score: R1, DB1, W1. Total = 3.
	Pharmaceutical industry support: Glaxo Group Research Ltd.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Study size	Low risk	Treatment groups > 200 participants

Goadsby 1991

Methods	Multicentre, randomised, double-blind, placebo-controlled, cross-over. Single dose to treat each of 4 successive attacks.
	Medication was administered as soon as participants were confident that they were having a migraine headache
	Assessment at 2 h after dosing
	Rescue medication available after 2 h
Participants	Aged 18 to 60, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity ≥ moderate) with an average of 1 to 6 attacks per month.
	Current prophylaxis was continued during the trial
	N = 61 (47 for efficacy)
	Proportion of male/female participants not reported
	Mean age 39 years
	Proportion with/without aura not reported
Interventions	Number of attacks in efficacy population
	Sumatriptan 100 mg, n = 94 (89 of moderate or severe intensity)
	Placebo, n = 94 (93 of moderate or severe intensity)
Outcomes	Headache relief (at 2 h)

Goadsby 1991 *(Continued)*

	Use of rescue medication
Notes	Oxford Quality Score: R1, DB2, W0. Total = 3. Pharmaceutical industry support: Glaxo Group Research Ltd.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Matching placebo
Study size	Unclear risk	Treatment groups 50 to 200 participants

Goadsby 2000

Methods	Multicentre, randomised, double-blind, double-dummy, placebo-controlled, parallel-group. Single dose to treat single attack. Medication administered when migraine headache pain was of moderate or severe intensity, and only if the aura phase had ended. Assessments at 0.5, 1, 1.5, and 2 h after dosing. Second blinded dose of study medication was available to treat recurrence within 24 h Rescue medication (analgesics, NSAIDs, or antiemetics) available as needed beginning 2 h after initial dosing
Participants	Aged 18 or over, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity ≥ moderate) with frequency of at least one attack every 6 weeks. Participants were excluded if they had more than 6 attacks per month No sumatriptan or any ergotamine-like compound within 48 h of taking study medication N = 692 M 124, F 568 (82%) Mean age 40 years Without aura 68%
Interventions	Sumatriptan 100 mg, n = 129 Eletriptan 20 mg, n = 144 Eletriptan 40 mg, n = 136 Eletriptan 80 mg, n = 141

Goadsby 2000 *(Continued)*

	Placebo, n = 142
Outcomes	Headache relief (at 1 and 2 h) Pain-free (at 1 and 2 h) Improvement in nausea and photo/phonophobia at 2 h Use of rescue medication Adverse events Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5. Pharmaceutical industry support: Pfizer Inc.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated pseudorandom code using method of random permuted blocks
Allocation concealment (selection bias)	Low risk	Study medication supplied pre-packed, dispensed as next consecutive number
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-dummy technique
Study size	Unclear risk	Treatment groups 50 to 200 participants

Goldstein 1998

Methods	Multicentre, randomised, double-blind, placebo-controlled, cross-over. Single dose to treat each of 2 successive attacks. Medication administered when migraine headache pain was of moderate or severe intensity Assessments at 0.5, 1, 2, 3, and 4 h after dosing Rescue medication available after 2 h for inadequate headache response Each treated attack was separated by a minimum of 5 days
Participants	Aged 18 to 91, meeting IHS criteria for migraine (1988) with or without aura. At least 6-month history of migraine (untreated severity ≥ moderate) with an average of 1 to 8 attacks per month. No monoamine oxidase inhibitors, propranolol, or lithium within 2 weeks; no sumatriptan, ergot derivatives, or opiates within 24 h; and no other form of analgesia or antiemetic within 6 h of taking study medication Standard migraine prophylaxis was permitted with the exception of NSAIDs and propranolol N = 1329 (1205 for efficacy) M 162, F 1167 (88%)

Goldstein 1998 *(Continued)*

	Mean age 40 years Without aura 89%
Interventions	Sumatriptan 25 mg, n = 563 Sumatriptan 50 mg, n = 566 Rizatriptan 5 mg, n = 557 Rizatriptan 10 mg, n = 567 Placebo, n = 141
Outcomes	Headache relief (at 1 and 2 h) Pain-free (at 1 and 2 h) Persistence of nausea, vomiting, photophobia, and phonophobia at 2 h Persistence of functional disability at 2 h Patients' opinion of treatment Use of rescue medication Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB1, W1. Total = 3. Pharmaceutical industry support: Merck Research Laboratories (supplies of sumatriptan provided by Glaxo Wellcome)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Study size	Unclear risk	Active treatment groups > 200 participants, placebo treatment group 141 participants

Goldstein 2005

Methods	Multicentre, randomised, double-blind, placebo-controlled, parallel-group. Single dose to treat single attack. Medication administered when the first symptoms usually recognised as the beginning of a migraine attack occurred

Goldstein 2005 *(Continued)*

	Assessment at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, and 4 h after dosing Rescue medication permitted, but no further details reported
Participants	Meeting IHS criteria for migraine (1988) with or without aura. At least 6-month history of migraine (untreated severity ≥ moderate) with an average of 1 to 8 attacks per month. Participants were excluded if their migraines were accompanied by vomiting more than 20% of the time or required bed rest for at least half of their attacks N = 171 (123 with moderate or severe baseline pain intensity) M 32, F 139 (81%) Mean age 38 years Without aura 14%
Interventions	Sumatriptan 50 mg, n = 67 Acetaminophen 1000 mg + aspirin 1000 mg + caffeine 260 mg combination, n = 69 Placebo, n = 35
Outcomes	Headache relief (at 1 and 2 h) Improvement in photophobia at 1.5 h Improvement in phonophobia at 2 h Improvement in functional disability at 4 h Patients' opinion of treatment Use of rescue medication Serious and specific adverse events
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5. Pharmaceutical industry support: Bristol-Myers Squibb

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation schedule
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Study medications were individually encapsulated to preserve study blinding
Study size	High risk	Active treatment groups 50 to 200 participants, placebo treatment group 35 participants

Gruffyd-Jones 2001

Methods	Multicentre, randomised double-blind, double-dummy, parallel-group. Single dose to treat each of up to 6 consecutive attacks. Medication administered when migraine headache pain was of moderate or severe intensity, provided a migraine-free period of at least 24 h had elapsed since the previous treated attack Assessments at 1, 2, 4, and 24 h after dosing Second dose of study medication available to treat recurrence between 2 and 24 h after the initial dosing Rescue medication (analgesics, NSAIDs, antiemetics, or sedatives) available after 2 h to treat persistent migraine headache. However, ergotamine derivatives not permitted until at least 6 h after initial dosing.
Participants	Aged 18 to 65, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity ≥ moderate) with an average of 1 to 6 attacks per month. Participants were excluded if they had suffered non-migraine headaches on more than 10 days per month over the preceding 6 months No monoamine oxidase inhibitors, methysergide, or methylergonovine within 2 weeks of randomisation N = 1666 (1522 for efficacy) M 223, F 1299 (85%) Mean age 42 years Without aura 57%
Interventions	Sumatriptan 50 mg, n = 555 (508 for efficacy) Zolmitriptan 2.5 mg, n = 551 (500 for efficacy) Zolmitriptan 5 mg, n = 560 (514 for efficacy)
Outcomes	Headache relief (at 1 and 2 h) Pain-free (at 1 and 2 h) 24-h sustained pain-free Improvement in nausea, photophobia, and phonophobia at 2 h Patients' opinion of treatment Use of rescue medication Adverse events Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5. Pharmaceutical industry support: AstraZeneca Pharmaceuticals

Risk of bias

Bias	Authors' judgement	Support for judgement

Gruffyd-Jones 2001 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer-generated random numbers scheme
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-dummy technique
Study size	Low risk	Treatment groups > 200 participants

Havanka 2000

Methods	Multicentre, randomised, double-blind, placebo-controlled, parallel-group. Single dose to treat single attack. Medication administered when migraine headache pain was of moderate or severe intensity Assessments at 10, 20, 30, 60, 90, 120, 180, and 240 minutes after dosing Rescue medication available 4 h after dosing for persistent headache
Participants	Aged 18 to 55, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity ≥ moderate) with an average of 1 to 6 attacks per month. No use of monoamine oxidase inhibitors, serotonin reuptake inhibitors, lithium, of flunarizine during the study period No sumatriptan or ergot-containing medications within 24 h before or after study drug administration, and no antiemetics or analgesics within 6 h of study drug administration Migraine prophylactic medication stopped at least 2 weeks before administration of study medication N = 643 (642 for efficacy) M 77, F 566 (88%) Mean age not reported Without aura 75%
Interventions	Sumatriptan 100 mg, n = 98 Naratriptan 1 mg, n = 85 Naratriptan 2.5 mg, n = 87 Naratriptan 5 mg, n = 93 Naratriptan 7.5 mg, n = 93 Naratriptan 10 mg, n = 96 (95 with moderate or severe baseline pain intensity) Placebo, n = 91
Outcomes	Headache relief (at 1 and 2 h) 24-h sustained headache relief Improvement in nausea and photo/phonophobia at 2 h

Havanka 2000 *(Continued)*

	Improvement in functional disability at 2 h
	Patients' opinion of treatment
	Use of rescue medication
	Adverse events
	Withdrawals
Notes	Oxford Quality Score: R2, DB1, W1. Total = 4.
	Pharmaceutical industry support: Glaxo Wellcome

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation numbers
Allocation concealment (selection bias)	Low risk	Numbers assigned in consecutive order, starting with the lowest available
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Study size	Unclear risk	Treatment groups 50 to 200 participants

Ishkanian 2007

Methods	Multicentre, randomised, double-blind, placebo-controlled, parallel-group. Single dose to treat single attack.
	Medication administered when migraine headache pain was of moderate or severe intensity
	Assessments at 0.5, 1, 2, and 4 h after dosing
	Rescue medication available after 2 h
Participants	Aged 18 to 65, suffering at least 6 self described or physician-diagnosed "sinus" headaches in the 6 months prior to screening which, upon careful review at screening, were determined to satisfy IHS diagnostic criteria for migraine (1988) with or without aura.
	Participants must have had no previous diagnosis of migraine and have had no previous use of migraine-specific medications, such as 5-$HT_{1B/1D}$ agonists, ergotamine, or ergot-like medications.
	Participants with evidence of other types of headache, such as chronic daily headache (more than 15 headache days per month), were excluded
	No monoamine oxidase inhibitors or sumatriptan within 2 weeks of trial screening. No analgesics, antiemetics, or other acute migraine medications, or sinus/nasal medications (e.g. antihistamines, nasal sprays and decongestants) within 24 h of taking study medication.
	N = 216 (215 for efficacy)
	M 64, F 151 (70%)
	Mean age 40 years

Ishkanian 2007 *(Continued)*

	Without aura 90%
Interventions	Sumatriptan 50 mg, n = 108 Placebo, n = 108 (107 for efficacy)
Outcomes	Headache relief (at 2 h) Pain-free (at 2 h) Improvement in nausea and photo/phonophobia at 2 h Use of rescue medication Adverse events Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5. Pharmaceutical industry support: GlaxoSmithKline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation schedules
Allocation concealment (selection bias)	Low risk	Remote allocation, assignments sealed and remained intact
Blinding (performance bias and detection bias) All outcomes	Low risk	Matching placebo
Study size	Unclear risk	Treatment groups 50 to 200 participants

Jelinski 2006

Methods	Multicentre, randomised, double-blind, double-dummy, placebo-controlled, parallel-group. Single dose to treat single attack. Medication administered within 2 h of the first sign of migraine pain, while the pain was still considered to be mild. Assessments at 0.5, 1, 2, 4, and 24 h after dosing Second dose of study medication available to treat recurrence 2 to 24 h after initial dosing Rescue medication (analgesics, antiemetics, or other acute migraine medications) were available after 2 h for inadequate symptom relief
Participants	Aged 18 to 65, meeting IHS criteria for migraine (1988) with or without aura. Had 1 to 6 migraine attacks per month in the 2 months prior to screening, and typically experienced moderate to severe migraine pain preceded by a mild pain phase. No use of monoamine oxidase inhibitors during the study period

Jelinski 2006 *(Continued)*

	No analgesics, antiemetics, or other acute migraine medications within 6 h of taking study medication. No ergotamine, ergot-type medications, or other $5HT_1$ agonists within 24 h of study medication use. Participants permitted to continue their use of prophylactic medications (excluding methysergide) during the study, provided the dose was stable for at least 1 month before study entry N = 361 M 52, F 309 (86%) Mean age 40 years Without aura 67%
Interventions	Sumatriptan 50 mg, n = 126 Sumatriptan 100 mg, n = 126 Placebo, n = 109
Outcomes	Pain-free (at 1 and 2 h) 24 h sustained pain-free Persistence of nausea, vomiting, photophobia, and phonophobia at 2 h (from SUM40291) Use of rescue medication (from SUM40291) Adverse events (with additional data from SUM40291) Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5. Pharmaceutical industry support: GlaxoSmithKline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation code
Allocation concealment (selection bias)	Low risk	Treatment group assignment was unknown to patients and investigators
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-dummy technique
Study size	Unclear risk	Treatment groups 50 to 200 participants

Kaniecki 2006

Methods	Multicentre, randomised, double-blind, placebo-controlled, parallel-group. Single dose to treat single attack. Medication administered when migraine headache pain was of moderate or severe intensity Assessments at 0.5, 1, 2, 4, and 24 h after dosing

Kaniecki 2006 *(Continued)*

	Second dose of study medication available after 2 h to treat recurrence or for pain if participant had at least a partial response to the first dose Alternative rescue medication (excluding ergotamine-containing medications and monoamine oxidase inhibitors) available after 2 h for persistent pain
Participants	Aged 18 to 65, self reporting tension/stress-type headache, who were given a diagnosis of migraine with or without aura according to IHS criteria (1988) at a screening visit. At least 1-year history of headache (untreated severity ≥ moderate) with an average of 1 to 6 attacks per month. Participants excluded if they had ever used a triptan, ergotamine, or an ergot derivative, or had persistent head or neck pain outside of migraine attacks (more than 15 days per month during the 2 months before screening) No monoamine oxidase inhibitors within 2 weeks of study entry N = 258 M 69, F 184 (73%) Mean age 37 years Proportion with/without aura not reported
Interventions	Sumatriptan 100 mg, n = 131 Placebo, n = 127
Outcomes	Headache relief (at 2 h) Pain-free (at 2 h) 24-h sustained headache relief 24-h sustained pain-free Patients' opinion of treatment Use of rescue medication Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB1, W1. Total = 3. Pharmaceutical industry support: GlaxoSmithKline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported

Kaniecki 2006 *(Continued)*

Study size	Unclear risk	Treatment groups 50 to 200 participants

Kolodny 2004

Methods	Multicentre, randomised, double-blind, placebo-controlled, cross-over. Single dose to treat each of 2 consecutive attacks. Medication administered when migraine headache pain was of moderate or severe intensity Assessments at 0.5, 1, 1.5, 2, 3, and 4 h after dosing Rescue medication (analgesics or antiemetics) was permitted from 2 h onwards in case of treatment failure or headache recurrence
Participants	Aged 18 years or older, meeting IHS criteria for migraine (1988) with or without aura. At least 6-month history of migraine (untreated severity ≥ moderate). No monoamine oxidase inhibitors, methysergide, or propranolol during the study period Standard antimigraine prophylactic medications (with the exception of NSAIDs, daily analgesics, or propanolol) were permitted N = 1447 (1287 for efficacy) M 203, F 1244 (86%) Mean age 40 years Proportion with/without aura not reported
Interventions	Sumatriptan 25 mg, n = 554 (290 1st attack only) Sumatriptan 50 mg, n = 550 (285 1st attack only) Rizatriptan 5 mg, n = 536 (288 1st attack only) Rizatriptan 10 mg, n = 547 (296 1st attack only) Placebo, n = 288
Outcomes	Headache relief (at 1 and 2 h) Pain-free (at 2 h) Persistence of nausea, vomiting, photophobia, and phonophobia at 2 h Persistence of functional disability at 2 h Use of rescue medication Adverse events
Notes	Oxford Quality Score: R2, DB2, W0. Total = 4. Pharmaceutical industry support: Merck & Co.

Risk of bias

Bias	Authors' judgement	Support for judgement

Kolodny 2004 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer-generated allocation schedule
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Matched placebos
Study size	Low risk	Treatment groups > 200 participants

Kudrow 2005

Methods	Multicentre, randomised, double-blind, double-dummy, placebo-controlled, parallel-group. Single dose to treat single attack. Medication administered when migraine headache pain was of moderate or severe intensity Assessments at 0.5, 1, 1.5, 2, 3, 4, 8, 12, and 24 h after dosing Second dose of study medication available if headache worsened, failed to improve or recurred within 24 h Rescue medication available 2 h after initial dosing (encouraged wait, not enforced)
Participants	Aged 18 to 65, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity ≥ moderate) with an average of 2 to 8 attacks per month, at least 2 of which were of moderate or severe intensity. Participants were only eligible for entry if they had previously used sumatriptan Changes to (or initiation of) migraine prophylactic medication less than 2 weeks before study screening visit were prohibited Chronic use (more than 3 days per week) of analgesics, COX-2 inhibitors, or non-specific NSAIDs not permitted No ergotamine-containing or ergot-type medication, 5-HT_{1D} or 5-$HT_{1B/1D}$ medication, or COX-2 inhibitors within 48 h of receiving study medication N = 574 M 48, F 526 (92%) Mean age 41 years Without aura 64%
Interventions	Sumatriptan 50 mg, n = 144 Valdecoxib 20 mg, n = 137 Valdecoxib 40 mg, n = 152 Placebo, n = 141
Outcomes	Headache relief (at 2 h) Improvement in nausea, vomiting, photophobia, and phonophobia at 2 h

Kudrow 2005 *(Continued)*

	Use of rescue medication
	Adverse events
	Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4.
	Pharmaceutical industry support: Pfizer Inc.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-dummy technique
Study size	Unclear risk	Treatment groups 50 to 200 participants

Latere 1991

Methods	Multicentre, randomised, double-blind, double-dummy, parallel-group. Single dose to treat each of 3 successive attacks.
	Assessment at 2 h
	Rescue medication available after 2 h
	Minimum of 48 h between treatments with trial medication
Participants	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity ≥ moderate) with an average of 1 to 6 attacks per month.
	All prophylactic therapy stopped at the initial screening visit
	N = 577
	M 98, F 479 (83%)
	Mean age 40 years
	Without aura 70%
Interventions	Sumatriptan (dispersible) 100 mg, n = 288 (220 with moderate or severe baseline pain intensity)
	Cafergot, n = 289 (246 with moderate or severe baseline pain intensity)
Outcomes	Headache relief (at 2 h)
	Pain-free (at 2 h)
	Improvement in nausea, vomiting, and photo/phonophobia at 2 h

Latere 1991 *(Continued)*

	Use of rescue medication
	Adverse events
	Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5.
	Pharmaceutical industry support: Glaxo Group Research Ltd.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation code
Allocation concealment (selection bias)	Low risk	Participants entered in ascending sequential order of patient number at each centre
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-dummy technique
Study size	Low risk	Treatment groups > 200 participants

Lines 2001

Methods	Multicentre, randomised, double-blind, placebo-controlled, parallel-group. Single dose to treat single attack.
	Medication administered when migraine headache pain was of moderate or severe intensity
	Assessments at 0.5, 1, 1.5, 2, 3, and 4 h after dosing
	Rescue medications, consisting of standard analgesics or antiemetics, were allowed from 2 h onwards
Participants	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 6-month history of migraine (untreated severity ≥ moderate) with an average of 1 to 8 attacks per month.
	No details of prohibited medications reported
	N = 792 (785 for efficacy)
	M 158, F 634 (80%)
	Mean age 40 years
	Proportion with/without aura not reported
Interventions	Sumatriptan 50 mg, n = 356
	Rizatriptan 5 mg, n = 349
	Placebo, n = 80
Outcomes	Headache relief (at 2 h)
Notes	Oxford Quality Score: R1, DB1, W0. Total = 2.

Lines 2001 *(Continued)*

	Pharmaceutical industry support: Merck & Co.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Study size	Unclear risk	Active treatment groups > 200 participants, placebo treatment group 80 participants

Lipton 2000

Methods	Multicentre, randomised, double-blind, placebo-controlled, cross-over. Single dose to treat each of up to 10 attacks. Medication administered when migraine headache pain was of moderate or severe intensity Assessments at 2, 3, and 24 h after dosing Rescue medication available after 4 h 24 h headache-free interval was required between treated headaches
Participants	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 6-month history of migraine (untreated severity ≥ moderate) with an average of 1 to 10 attacks per month. Participants with clinical diagnosis of migrainous headache and episodic tension-type headache were also included in the study, although only those with IHS-diagnosed migraine were used for efficacy analysis Participants were required to have an HIQ score of 250 or greater at screening No monoamine oxidase inhibitor use during the study period N = 311 (249 with migraine diagnosis for efficacy) M 35, F 214 (86%) Mean age 38 years Proportion with/without aura not reported Total number of treated attacks = 1110
Interventions	Treated attacks: Sumatriptan 50 mg, n = 870 Placebo, n = 240
Outcomes	Headache relief (at 2 h)

Lipton 2000 *(Continued)*

	Pain-free (at 2 h)
	Use of rescue medication
	Adverse events
	Withdrawals
Notes	Oxford Quality Score: R2, DB2, W0. Total = 4.
	Pharmaceutical industry support: Glaxo Wellcome

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical appearing placebo
Study size	Low risk	Treatment groups > 200 participants

Mathew 2003

Methods	Multicentre, randomised, double-blind, double-dummy, placebo-controlled, parallel-group. Single dose to treat single attack.
	Medication administered when migraine headache pain was of moderate or severe intensity
	Assessments at 0.5, 1, 1.5, 2, 4, and 24 h after dosing
	Second dose of study medication available to treat recurrence after 2 h
	Rescue medication available after 2 h for inadequate headache relief, although participants not permitted to take any other triptan, ergotamine, or ergotamine-like substance for 24 h after initial dosing
Participants	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura and a monthly frequency of 1 to 6 attacks.
	No use of potent CYP3A4 inhibitors or monoamine oxidase inhibitors within 2 weeks prior to study entry.
	No analgesic or antiemetic within 6 h, or triptan, ergotamine-containing or ergot-type medication within 48 h of taking study medication
	N = 2113 (2072 for efficacy)
	M 277, F 1795 (87%)
	Mean age 42 years
	Without aura 65%
Interventions	Sumatriptan 100 mg, n = 831

Mathew 2003 *(Continued)*

	Eletriptan 40 mg, n = 822
	Placebo, n = 419
Outcomes	Headache relief (at 1 and 2 h)
	Pain-free (at 1 and 2 h)
	24-h sustained headache relief
	Improvement in nausea, photophobia, and phonophobia at 2 h
	Improvement in functional disability at 2 h
	Use of rescue medication
	Adverse events
	Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4.
	Pharmaceutical industry support: Pfizer Ltd.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-dummy technique
Study size	Low risk	Treatment groups > 200 participants

Myllyla 1998

Methods	Multicentre, randomised, double-blind, double-dummy, placebo-controlled, parallel-group. Up to 2 doses to treat each of 2 successive attacks.
	Medication administered at the first symptoms of a migraine attack
	Assessment at 2 h
	Second dose of study medication if headache not improved after 1 h
	Alternative rescue medication (paracetamol, acetylsalicylic acid, naproxen, ketoprofen, prochlorperazine, or diazepam) available after 2 h if headache relief still insufficient
	At least 48 h required between the treatment of 2 successive attacks
Participants	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity ≥ moderate) with an average of 1 to 4 attacks per month.
	N = 154 (126 for efficacy)

Myllyla 1998 *(Continued)*

	M 15, F 126 (89%) Mean age 39 years Without aura 72%
Interventions	Sumatriptan 100 mg (+ optional dose of placebo after 1 h), n = 46 (42 for efficacy) Tolfenamic acid 200 mg (+ optional 2nd dose after 1 h), n = 47 (43 for efficacy) Placebo (+ optional dose of placebo after 1 h), n = 46 (41 for efficacy)
Outcomes	Headache relief (at 2 h) Pain-free (at 2 h) Improvement in nausea, vomiting, photophobia, and phonophobia at 2 h Use of rescue medication Adverse events
Notes	Oxford Quality Score: R2, DB2, W0. Total = 4. Pharmaceutical industry support: A/S GEA Farmaceutisk Fabrik (medication used was Imigran)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation code
Allocation concealment (selection bias)	Low risk	Complete randomisation blocks assigned to centres, participants entered in ascending sequential order of patient number
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-dummy technique
Study size	High risk	Treatment groups < 50 participants

Nappi 1994

Methods	Multicentre, randomised, double-blind, placebo-controlled, parallel-group. Single dose to treat single attack. Medication administered at the first sign of migraine Assessments at 2 and 4 h Second dose of study medication available if symptom relief was inadequate at 2 h Alternative rescue medication (not ergotamine) was available if the response after 4 h was still inadequate Headache recurrence after either the first or second dose could be treated by a third dose of study medication, providing it was more than 2 h after the most recent dose and less than 24 h after the first dose

Nappi 1994 *(Continued)*

Participants	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity ≥ moderate). Participants were excluded if they were taking migraine prophylaxis N = 250 (244 for efficacy) M 56, F 188 (77%) Mean age 38 years Without aura 87%
Interventions	Sumatriptan 100 mg, n = 158 (148 with moderate or severe baseline pain intensity) Placebo, n = 86 (81 with moderate or severe baseline pain intensity)
Outcomes	Headache relief (at 2 h) Pain-free (at 2 h) Improvement in nausea, vomiting, and photo/phonophobia at 2 h Patients' opinion of treatment Use of second dose of study medication Use of rescue medication Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB1, W1. Total = 3. Pharmaceutical industry support: Glaxo Group Research Ltd.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Study size	Unclear risk	Treatment groups 50 to 200 participants

Nett 2003

Methods	Multicentre, randomised, double-blind, placebo-controlled, parallel-group. Single dose to treat single menstrually associated migraine attack. Medication administered within 1 h of the onset of pain, but only if the pain was mild at onset and only if the pain was still mild at the time of treatment

Nett 2003 *(Continued)*

	Assessments at 0.5, 1, and 2 h after dosing Rescue medication or a second double-blind dose of study medication were available to treat either inadequate response after 2 h or recurrence between 2 and 24 h
Participants	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine with a minimum of 6 months of regularly occurring menstrually associated migraines (defined as occurring between day -2 to day 4 relative to the first day of flow). Participants had to have had menstrually associated migraine in at least 2 of their last 3 perimenstrual periods before screening that were typically associated with moderate to severe pain preceded by a mild pain phase Participants were excluded if they had tension-type headache for more than 15 days per month or more than 6 migraine attacks per month in either of the 2 months before screening No monoamine oxidase inhibitors or ergotamine-containing or ergotamine-type migraine prophylactic medication during the study period. Other migraine prophylactic medications were permitted, provided they had been on a constant regimen for at least 1 month before screening and the regimen remained constant throughout the study. No analgesics, antiemetics, or non-serotonin-agonist acute migraine medications within 6 h of taking study medication N = 369 (368 for efficacy, 349 for per-protocol efficacy) All F Mean age 36 years Without aura 75%
Interventions	Sumatriptan 50 mg, n = 124 (124 for efficacy, 116 for per-protocol efficacy) Sumatriptan 100 mg, n = 122 (122 for efficacy, 115 for per-protocol efficacy) Placebo, n = 123 (122 for efficacy, 118 for per-protocol efficacy)
Outcomes	Pain-free (at 1 and 2 h) 24-h sustained pain-free Persistence of nausea and photo/phonophobia at 2 h Improvement in functional disability at 2 h (from Landy 2004 (secondary reference for this study) Study 2) Adverse events Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5. Pharmaceutical industry support: GlaxoSmithKline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation schedule

Nett 2003 *(Continued)*

Allocation concealment (selection bias)	Low risk	Remote allocation
Blinding (performance bias and detection bias) All outcomes	Low risk	All tablets were visually indistinguishable
Study size	Unclear risk	Treatment groups 50 to 200 participants

Patten 1991

Methods	Multicentre, randomised, double-blind, placebo-controlled, parallel-group. Single dose to treat each of up to 3 successive attacks. Medication administered at the earliest sign of a migraine attack, provided at least 48 h had elapsed since the previous study treatment. Assessment at 2 h after dosing Rescue medication (excluding ergotamine-containing medication) was available after 2 h if symptoms were not adequately relieved
Participants	Aged 18 to 60 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity ≥ moderate) with an average of 1 to 6 attacks per month. All use of prophylactic migraine therapy was stopped at least 2 weeks before starting on the study medication N = 624 (538 with moderate or severe baseline pain intensity) No demographic data given
Interventions	Sumatriptan (dispersible) 100 mg, n = 142 Sumatriptan (dispersible) 200 mg, n = 140 Sumatriptan (dispersible) 300 mg, n = 155 Placebo, n = 101
Outcomes	Headache relief (at 2 h) Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB1, W0. Total = 2. Pharmaceutical industry support: Glaxo Group Research Ltd.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported

Patten 1991 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Study size	Unclear risk	Treatment groups 50 to 200 participants

Pfaffenrath 1998

Methods	Multicentre, randomised, double-blind, placebo-controlled, parallel-group. Single dose to treat each of 3 separate attacks. Assessment at 0.5, 1, 2, 3, and 4 h after dosing Second randomised dose of study medication available to treat headache recurrence from 2 to 24 h after initial dosing Rescue medication (excluding ergotamine-containing preparations or sumatriptan) was permitted if headache relief was inadequate 4 h after initial dosing
Participants	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity ≥ moderate) with an average of 1 to 6 attacks per month. No use of lithium, monoamine oxidase inhibitors, serotonin reuptake inhibitors, or ergotamine-containing migraine prophylactic medications during the study period No analgesics or antiemetics within 6 h and no ergotamine-containing medications within 24 h of taking study medication N = 1003 (939 with moderate or severe baseline pain intensity) M 157, F 846 (84%) Mean age 40 years Without aura 66%
Interventions	Sumatriptan 25 mg, n = 303 (286 with moderate or severe baseline pain intensity) Sumatriptan 50 mg, n = 303 (285 with moderate or severe baseline pain intensity) Sumatriptan 100 mg, n = 298 (277 with moderate or severe baseline pain intensity) Placebo, n = 99 (91 with moderate or severe baseline pain intensity)
Outcomes	Headache relief (at 1 and 2 h) Pain-free (at 2 h) Improvement in nausea and photo/phonophobia at 2 h Persistence of functional disability at 2 h Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4.

Pfaffenrath 1998 *(Continued)*

	Pharmaceutical industry support: Glaxo Wellcome

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Matching placebo
Study size	Unclear risk	Active treatment groups > 200 participants, placebo treatment group 99 participants

Pini 1999

Methods	Multicentre, 2 phase study Phase 1: Randomised, open-label treatment of a single attack with 1 of 3 standard over-the-counter migraine medications when migraine headache pain was of mild or moderate intensity. Participants who failed to respond in phase 1 then went on to phase 2. Phase 2: Randomised, double-blind, placebo-controlled, parallel-group. Single dose to treat single attack. Medication was administered when migraine headache pain was of mild or moderate intensity. Assessments at 2 and 4 h after dosing Second dose of study medication was available to treat recurrence between 4 and 24 h Rescue medication was available for insufficient relief of symptoms 4 h after initial dosing
Participants	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity mild or moderate) with an average of 1 to 8 attacks per month. No migraine prophylaxis containing ergotamine during the study period No sumatriptan or ergotamine-containing drugs within 24 h, or other analgesics or antiemetics within 6 h of taking study medication Phase 2: N = 219 (167 for efficacy) M 44, F 175 (80%) Mean age 37 years Proportion with/without aura not reported
Interventions	Sumatriptan 50 mg, n = 137 (106 for efficacy)

Pini 1999 *(Continued)*

	Placebo, n = 82 (61 for efficacy)
Outcomes	Pain-free (at 2 h) Use of rescue medication Adverse events
Notes	Oxford Quality Score: R1, DB1, W0. Total = 2. Pharmaceutical industry support: Glaxo Wellcome (medication used was Imigran)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Study size	Unclear risk	Treatment groups 50 to 200 participants

Pini 1995

Methods	Multicentre, randomised, double-blind, placebo-controlled, parallel-group. Single dose to treat single attack. Medication administered at the earliest sign of migraine attack Assessments every 30 minutes up to 4 h, and then every 6 h up to 48 h after dosing Rescue medication (ergotamine-free) was available after 4 h if the headache was not controlled
Participants	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 6-month history of migraine (untreated severity ≥ moderate). No details of prohibited medications reported. N = 238 (222 for efficacy) M 52, F 186 (78%) Mean age 37 years Without aura 61%
Interventions	Sumatriptan 100 mg, n = 151 Placebo, n = 87
Outcomes	All efficacy data at 4 h Adverse events

Pini 1995 *(Continued)*

Notes	Oxford Quality Score: R1, DB1, W0. Total = 2. Pharmaceutical industry support: Glaxo

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Study size	Unclear risk	Treatment groups 50 to 200 participants

Sandrini 2002

Methods	Multicentre, randomised, double-blind, double-dummy, placebo-controlled, parallel-group. Single dose to treat each of up to 3 successive attacks. Medication administered within 6 h of onset of a migraine attack, when the headache pain was of moderate or severe intensity, and if any aura phase had ended Assessments at 0.5, 1, 2, 4, and 24 h after dosing Second, blinded and randomised dose of study medication was available if there was no response to treatment after 2 h, or if there was a recurrence of headache within 24 h Rescue medication was available 2 h after the second dose if there was still no improvement in headache
Participants	Aged 18 years or older, meeting IHS criteria for migraine (1988) with or without aura, and suffering at least 1 attack every 6 weeks. Participants were excluded if they had previously taken oral eletriptan or any formulation of sumatriptan. No ergotamine or any ergotamine-like agent within 48 h before, or 24 h after, taking study medication. No proprietary analgesic or antiemetic within 6 h of taking study medication. N = 774 M 93, F 681 (88%) Mean age 38 years Without aura 65%
Interventions	Sumatriptan 50 mg, n = 181 Sumatriptan 100 mg, n = 170 Eletriptan 40 mg, n = 175 Eletriptan 80 mg, n = 164

Sandrini 2002 *(Continued)*

	Placebo, n = 84
Outcomes	Headache relief (at 1 and 2 h) Pain-free (at 1 and 2 h) 24-h sustained headache relief 24-h sustained pain-free Improvement in nausea, photophobia, and phonophobia at 2 h Improvement in functional disability at 2 h Use of rescue medication Serious and specific adverse events Withdrawals due to adverse events
Notes	Oxford Quality Score: R1, DB2, W0. Total = 3. Pharmaceutical industry support: Pfizer Ltd.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-dummy technique
Study size	Unclear risk	Treatment groups 50 to 200 participants

Sandrini 2007

Methods	Multicentre, randomised, double-blind, double-dummy, placebo-controlled, parallel-group. Single dose to treat each of 2 consecutive attacks separated by at least 48 h. Medication administered when migraine headache pain was of moderate or severe intensity Assessments at 0.5, 1, 1.5, 2, 3, 4, and 5 h after dosing Second dose of study medication available as rescue medication after 2 h if headache relief was inadequate, or to treat recurrence within 48 h of initial dosing Alternative rescue medication was available 2 h after the second dose if headache relief remained inadequate. Ergot derivatives and opiates could not be used as a rescue medication.
Participants	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity ≥ moderate) and suffering an average of 1 to 6 attacks per month. Use of migraine prophylaxis or ergot derivatives during the month of screening and the study period was prohibited

Sandrini 2007 *(Continued)*

	Participants were not permitted to take coffee or beverages containing caffeine during the migraine attack
	N = 282 (281 for efficacy)
	M 61, F 220 (78%)
	Mean age 35 years
	Without aura 93%
Interventions	Sumatriptan 50 mg, n = 139 (138 for efficacy)
	Indoprocaf (indomethacin 25 mg + prochlorperazine 2 mg + caffeine 75 mg), n = 143
Outcomes	Headache relief (at 2 h)
	Pain-free (at 1 and 2 h)
	24-h sustained headache relief
	24-h sustained pain-free
	Improvement in nausea, vomiting, photophobia, and phonophobia at 2 h
	Use of rescue medication
	Adverse events
	Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5.
	Pharmaceutical industry support: Solvay Pharma

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated code list
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-dummy technique
Study size	Unclear risk	Treatment groups 50 to 200 participants

Sargent 1995

Methods	Multicentre, randomised, double-blind, placebo-controlled, parallel-group. Single dose to treat single attack.
	Medication administered when migraine headache pain was of moderate or severe intensity
	Assessments every 30 mins up to 4 h after dosing

Sargent 1995 *(Continued)*

	Rescue medication (acetaminophen) available after 2 h if pain had not improved relative to predose levels. Rescue medication other than acetaminophen was allowed beginning 4 h after initial dosing.
Participants	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity ≥ moderate) and suffering an average of 1 to 6 attacks per month. Migraine prophylaxis was not allowed during the 2-week period preceding treatment No simple analgesics during 6 h preceding treatment, and no opioid-containing agents or ergotamine during the 24 h preceding treatment N = 187 M 16, F 171 (91%) Mean age 40 years Without aura 80%
Interventions	Sumatriptan 25 mg, n = 48 Sumatriptan 50 mg, n = 46 Sumatriptan 100 mg, n = 46 Placebo, n = 47
Outcomes	Headache relief (at 1 and 2 h) Improvement in nausea and photophobia at 2 h Improvement in functional disability at 2 h Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB1, W1. Total = 3. Pharmaceutical industry support: Glaxo Research Institute

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Study size	High risk	Treatment groups < 50 participants

Savani 1999

Methods	Multicentre, randomised, double-blind, placebo-controlled, parallel-group. Single dose to treat each of up to 3 separate attacks. Assessments at 0.5, 1, 2, 3, and 4 h after dosing. Second dose of study medication available to treat recurrence from 4 to 24 h after initial dosing Rescue medication (excluding ergotamine-containing preparations or sumatriptan) was permitted if headache relief was inadequate 4 h after taking study medication
Participants	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity ≥ moderate) and suffering an average of 1 to 6 attacks per month. Participants were excluded if they had ever taken sumatriptan previously or were currently using a monoamine oxidase inhibitor, a serotonin reuptake inhibitor, or lithium No analgesics or antiemetics within 6 h, or ergotamine or ergotamine-containing medication within 24 h of taking study medication. Normal prophylactic medication for migraine was permitted (unchanged throughout the study, if possible) N = 485 (less than 1% of which had mild pain at baseline) M 68, F 417 (86%) Mean age 36 to 40 years Without aura 67% to 87%
Interventions	Sumatriptan 50 mg, n = 331 Placebo, n = 154
Outcomes	Headache relief (at 1 and 2 h) Pain-free (at 2 h) Adverse events
Notes	Oxford Quality Score: R1, DB1, W0. Total = 2. Pharmaceutical industry support: Glaxo Wellcome

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Study size	Unclear risk	Active treatment group > 200 participants, placebo treatment group 154 participants

Schulman 2003

Methods	Single centre, randomised, double-blind, cross-over. Each participant treated 2 successive attacks with a single dose, one with each study treatment. Medication administered when migraine headache pain was of moderate or severe intensity Assessments at 30, 60, 90, and 120 minutes after dosing
Participants	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura, and suffered an average of 1 to 8 attacks per month Participants were only eligible for entry if they had failed to receive adequate self defined relief from triptans previously, had at least 15 headache-free days per month, and did not experience vomiting in greater than 25% of their migraine attacks Migraine prophylaxis was permitted, provided the dose of the medications had been stable for at least 30 days before initiating the trial N = 18 (16 for efficacy) M 3, F 13 (81%) Mean age 40 years Without aura 81%
Interventions	Sumatriptan 50 mg, n = 16 Sumatriptan 50 mg + metoclopramide 10 mg, n = 16
Outcomes	Headache relief (at 2 h) Improvement in nausea, photophobia, and phonophobia at 2 h Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4. Pharmaceutical industry support: GlaxoSmithKline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical pills
Study size	High risk	Treatment groups < 50 participants

Sheftell 2005

Methods	Two identically designed studies, multicentre, randomised, double-blind, placebo-controlled, parallel-group. Single dose to treat single attack. Medication administered when migraine headache pain was of moderate or severe intensity Assessments every 10 minutes for the first 2 h, and then at 4 and 24 h after dosing Second dose of study medication or non-prohibited acute migraine medication available after 2 h to treat recurrence Rescue medication available after 2 h if pain not reduced to mild or none within 2 h after initial dosing
Participants	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 6-month history of migraine (untreated severity ≥ moderate) and suffering an average of 1 to 6 attacks per month. Participants were excluded if they experienced headache on more than 15 days per month in any of the 3 months before screening. No migraine prophylactic medication containing ergotamine, an ergot derivative, or methysergide, or use of monoamine oxidase inhibitor within 2 weeks before screening. Study 1: N = 1477 (1366 for efficacy) M 196, F 1170 (86%) Mean age 41 years Without aura 70% Study 2: N = 1475 (1330 for efficacy) M 204, F 1126 (85%) Mean age 40 years Without aura 67%
Interventions	Study 1: Sumatriptan (rapid-release) 50 mg, n = 494 (448 for efficacy) Sumatriptan (rapid-release) 100 mg, n = 488 (462 for efficacy) Placebo, n = 495 (456 for efficacy) Study 2: Sumatriptan (rapid-release) 50 mg, n = 496 (454 for efficacy) Sumatriptan (rapid-release) 100 mg, n = 485 (440 for efficacy) Placebo, n = 494 (436 for efficacy)
Outcomes	Headache relief (at 2 h) Pain-free (at 2 h) 24-h sustained headache relief 24-h sustained pain-free

Sheftell 2005 *(Continued)*

	Use of rescue medication
	Adverse events
	Withdrawals
Notes	Oxford Quality Score: R1, DB1, W1. Total = 3.
	Pharmaceutical industry support: GlaxoSmithKline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	Remote allocation generated by the study sponsor and not available to the investigators
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Study size	Low risk	Treatment groups > 200 participants

Smith 2005

Methods	Multicentre, randomised, double-blind, double-dummy, placebo-controlled, parallel-group. Single dose to treat single attack.
	Medication administered when migraine headache pain was of moderate or severe intensity
	Assessments every 15 minutes up to 2 h, every 30 minutes between 2 and 4 h and hourly between 4 and 24 h after dosing
	Rescue medication available after 2 h
Participants	Aged 18 years or older, meeting IHS criteria for migraine (1988 and 2004) with or without aura. At least 1-year history of migraine (untreated severity ≥ moderate) and suffering an average of 2 to 6 attacks per month.
	Participants had a history of tolerating oral treatment with a 5-HT agonist for migraine
	N = 972 (965 for efficacy)
	M 92, F 880 (91%)
	Mean age 42 years
	Without aura 75%
Interventions	Sumatriptan 50 mg, n = 229 (226 for efficacy)
	Sumatriptan 50 mg, + naproxen 500 mg, n = 251 (250 for efficacy)
	Naproxen 500 mg, n = 250 (248 for efficacy)
	Placebo, n = 241

Smith 2005 *(Continued)*

Outcomes	Headache relief (at 1 and 2 h) Pain-free (at 1 and 2 h) 24-h sustained headache relief 24-h sustained pain-free Persistence of nausea, photophobia, and phonophobia at 2 h Use of rescue medication Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4. Pharmaceutical industry support: Pozen Inc.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-dummy technique
Study size	Low risk	Treatment groups > 200 participants

Spierings 2001

Methods	Multicentre, randomised, double-blind, parallel-group. Single dose to treat single attack. Medication administered when migraine headache pain was of moderate or severe intensity Assessments at 0.5, 1, 2, 4, 24, and 48 h after dosing Second dose of study medication available to treat recurrence between 2 and 24 h Rescue medication (excluding triptans or ergotamine) available 2 h after taking study medication if migraine pain had not decreased to mild or none
Participants	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 6-month history of migraine (untreated severity ≥ moderate) and suffering at least 2 attacks per month, with a minimum interval of 24 h between consecutive attacks. Preventative migraine treatment was allowed, with the exception of monoamine oxidase inhibitors, lithium carbonate, cyproheptadine hydrochloride, methysergide maleate, ergotamine tartrate, and dihydroergotamine mesylate which had to be discontinued at least 2 weeks before enrolment. Participants were excluded if they had ever taken almotriptan before, but could not be triptan naive N = 1173

Spierings 2001 *(Continued)*

	M 129, F 1044 (89%)
	Mean age 41 years
	Proportion with/without aura not reported
Interventions	Sumatriptan 50 mg, n = 582
	Almotriptan 12.5 mg, n = 591
Outcomes	Headache relief (at 1 and 2 h)
	Pain-free (at 1 and 2 h)
	Improvement in nausea, vomiting, photophobia, and phonophobia at 2 h
	Use of rescue medication
	Adverse events
	Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4.
	Pharmaceutical industry support: Pharmacia

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical-looking capsules
Study size	Low risk	Treatment groups > 200 participants

Tfelt-Hansen 1995

Methods	Multicentre, randomised, double-blind, double-dummy, placebo-controlled, parallel-group. Single dose to treat each of 2 consecutive attacks.
	Medication administered when migraine headache pain was of moderate or severe intensity
	Assessments at 2 and 24 h after dosing
	Rescue medication (except for ergot alkaloids or morphinomimetic drugs) was allowed if the headache was inadequately controlled after 2 h
Participants	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity ≥ moderate) and suffering an average of 2 to 6 attacks per month.
	N = 389 (385 for efficacy)
	M 94, F 327 (78%)

Tfelt-Hansen 1995 *(Continued)*

	Mean age 39 years
	Without aura 85%
Interventions	Sumatriptan 100 mg, n = 122
	Lysine acetylsalicylate 1620 mg + metoclopramide 10 mg, n = 137
	Placebo, n = 126
Outcomes	Headache relief (at 2 h)
	Improvement in nausea and vomiting at 2 h
	Patients' opinion of treatment
	Use of rescue medication
	Adverse events
	Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4.
	Pharmaceutical industry support: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-dummy technique
Study size	Unclear risk	Treatment groups 50 to 200 participants

Tfelt-Hansen 1998

Methods	Multicentre, randomised, double-blind, triple-dummy, placebo-controlled, parallel-group. Single dose to treat single attack.
	Medication administered when migraine headache pain was of moderate or severe intensity
	Assessments at 0.5, 1, 1.5, 2, 3, and 4 h after dosing
	Rescue medication was available to treat non-response at 2 h, or recurrence within 24 of initial dosing. Sumatriptan, Midrin, and ergot derivatives were prohibited as rescue medications until 24 after initial dosing.
Participants	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 6-month history of migraine (untreated severity ≥ moderate) and suffering an average of 1 to 8 attacks per month.
	Participants were excluded if they had ever been exposed to rizatriptan before

Tfelt-Hansen 1998 *(Continued)*

	No monoamine oxidase inhibitors, methysergide, or lithium within 2 weeks; sumatriptan, Midrin, or ergot derivatives within 48 h; any opiate within 24 h; or any other form of analgesia or antiemetic within 6 h of taking study medication Standard migraine prophylaxis was permitted with the exception of NSAIDs N = 1099 M 201, F 898 (82%) Mean age 38 years Without aura 84%
Interventions	Sumatriptan 100 mg, n = 388 Rizatriptan 5 mg, n = 164 Rizatriptan 10 mg, n = 387 Placebo, n = 160
Outcomes	Headache relief (at 1 and 2 h) Pain-free (at 1 and 2 h) Improvement in nausea, photophobia, and phonophobia at 2 h Improvement in functional disability at 2 h Use of rescue medication Adverse events Withdrawals due to adverse events
Notes	Oxford Quality Score: R2, DB2, W0. Total = 4. Pharmaceutical industry support: Merck & Co.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated schedule
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Triple-dummy technique
Study size	Unclear risk	Some active treatment groups > 200 participants, others and placebo treatment group 50 to 200 participants

Tfelt-Hansen 2006

Methods	Multicentre, randomised, double-blind, placebo-controlled, parallel-group. Single dose to treat single attack. Medication administered within 1 h after the start of an attack, but only if the attack was still in the mild headache phase Assessments at 0.5, 1, and 2 h after dosing Second dose available to treat recurrence between 2 and 24 h Rescue medication available after 2 h if pain relief was incomplete. However, triptans or ergotamine could not be used as rescue medication within 24 of taking study medication.
Participants	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine, in which attacks became moderate or severe following an initial mild pain phase, and suffered a total of 6 to 12 attacks per year. Participants were excluded if they had treated a migraine with a triptan within the last 6 months. N = 101 M 22, F 79 (78%) Mean age 38 years Without aura 80%
Interventions	Sumatriptan 50 mg, n = 53 Placebo, n = 48
Outcomes	Pain-free (at 2 h) 24-h sustained pain-free Patients' opinion of treatment Adverse events
Notes	Oxford Quality Score: R1, DB1, W1. Total = 3. Pharmaceutical industry support: GlaxoSmithKline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Study size	High risk	Active treatment group 50 to 200 participants, placebo treatment group < 50 participants

Thomson 1992

Methods	Multicentre, randomised, double-blind, double-dummy, parallel-group. Single dose to treat each of up to 3 separate attacks. Assessment at 2 h after dosing. Rescue medication (not containing ergotamine, aspirin or metoclopramide) available after 2 h for inadequate headache response Minimum interval of 48 h between consecutive study treatments
Participants	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine (untreated severity ≥ moderate) and suffering an average of 1 to 6 attacks per month. All migraine prophylaxis was discontinued at least 2 weeks prior to the use of study medication No ergotamine-containing medication within 24 h of taking study medication N = 358 (316 for efficacy) M 72, F 283 (80%) Mean age 41 years Without aura 64%
Interventions	Sumatriptan 100 mg, n = 175 (153 with moderate or severe baseline pain intensity) Aspirin 900 mg + metoclopramide 10 mg, n = 183 (163 with moderate or severe baseline pain intensity)
Outcomes	Headache relief (at 2 h) Pain-free (at 2 h) Improvement in nausea, vomiting, and photo/phonophobia at 2 h Patients' opinion of treatment Use of rescue medication Adverse events Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5. Pharmaceutical industry support: Glaxo Group Research Ltd.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation code
Allocation concealment (selection bias)	Low risk	Complete randomisation blocks allocated to centres and participants assigned in order of registration for study
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-dummy technique

Thomson 1992 *(Continued)*

Study size	Unclear risk	Treatment groups 50 to 200 participants

Visser 1996

Methods	Multicentre, randomised, double-blind, placebo-controlled, parallel-group. Single dose to treat single attack. Medication administered when migraine headache pain was of moderate or severe intensity Assessments at 0.5, 1, 1.5, and 2 h after dosing Second, blinded dose of study medication available after 2 h for inadequate headache response Rescue medication (opiates, acetaminophen, or NSAIDs) available after 4 h, and sumatriptan or ergotamine-derivatives available after 24 h
Participants	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 6-month history of migraine (untreated severity ≥ moderate) and suffering 8 or fewer migraine attacks per month. No fluoxetine hydrochloride within 6 weeks, prophylactic antimigraine treatment within 2 weeks, ergot derivatives or sumatriptan within 48 h, opiate within 24 h, or any other form of analgesia within 6 h of taking study medication N = 449 M 47, F 402 (90%) Mean age 40 years Proportion with/without aura not reported
Interventions	Sumatriptan 100 mg, n = 72 Rizatriptan 10 mg, n = 89 Rizatriptan 20 mg, n = 82 Rizatriptan 40 mg, n = 121 Placebo, n = 85
Outcomes	Headache relief (at 1 and 2 h) Pain-free (at 2 h) Persistence of functional disability at 2 h Use of rescue medication Adverse events Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4. Pharmaceutical industry support: Merck Research Laboratories

Risk of bias

Bias	Authors' judgement	Support for judgement

Visser 1996 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Matching capsules
Study size	Unclear risk	Treatment groups 50 to 200 participants

Winner 2003

Methods	Two identical studies, multicentre, randomised, double-blind, double-dummy, placebo-controlled, parallel-group. Single dose to treat single attack. Medication administered at the first sign of pain, while the pain was mild Assessments at 0.5, 1, 2, 4, and 24 h after dosing Second dose of study medication available to treat recurrence between 2 and 24 h after initial dosing Rescue medication (analgesics, antiemetics, or other acute migraine medications) available 4 h after initial dosing
Participants	Aged 18 to 65 years, meeting IHS criteria for migraine (1988) with or without aura. At least 1-year history of migraine with an average of 1 to 6 attacks per month. All participants were required to experience moderate or severe migraine pain preceded by a mild pain phase. No use of monoamine oxidase inhibitors for a minimum of 2 weeks before screening or throughout the course of the study. Otherwise allowed to continue migraine prophylactic medications. No analgesics, antiemetics, or other migraine medication within the 6 h before taking study medication, and no ergotamine, ergot-type medications, or other serotonin$_{1B/1D}$ agonists within 24 h of study medication use Study 1: N = 362 (354 for efficacy, of which 3% did not have mild pain at baseline) M 43, F 311 (88%) Mean age 41 years Without aura 73% Study 2: N = 354 (337 for efficacy, of which 4 % did not have mild pain at baseline) M 59, F 298 (88%) Mean age 43 years Without aura 79%
Interventions	Study 1: Sumatriptan 50 mg, n = 122

Winner 2003 *(Continued)*

	Sumatriptan 100 mg, n = 115 Placebo, n = 117 Study 2: Sumatriptan 50 mg, n = 111 Sumatriptan 100 mg, n = 107 Placebo, n = 119
Outcomes	Pain-free (at 1 and 2 h) Improvement in nausea, photophobia, and phonophobia at 2 h Use of rescue medication Adverse events
Notes	Oxford Quality Score: R2, DB2, W0. Total = 4. Pharmaceutical industry support: GlaxoSmithKline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation schedule
Allocation concealment (selection bias)	Low risk	Treatment assignment sealed and remained intact throughout the study
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-dummy technique
Study size	Unclear risk	Treatment groups 50 to 200 participants

DB: double-blinding; F: female; h: hour; HIQ: Headache Impact Questionnaire; IHS: International Headache Society; M: male; NSAID: non-steroidal anti-inflammatory drug; R: randomisation; W: withdrawals

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

Study	Reason for exclusion
Cady 1994	First dose of subcutaneous sumatriptan not randomised, only for subsequent doses of oral sumatriptan for recurrence (from 2 to 24 h after initial dosing) were patients randomised to either sumatriptan or placebo
Cady 2000	Insufficient number of participants in placebo group (≤ 10)
Centonze 1995	No IHS diagnosis
Colman 2001	No useable outcomes reported

Study	Reason for exclusion
Dowson 2000	No IHS diagnosis of migraine - attacks were GP diagnosed with no subsequent re-analysis according to IHS criteria
Dowson 2005	No useable data - only 4 h data reported and number of patients analysed for particular outcome uninterpretable
Ferrari 1994	First dose of sumatriptan not randomised, only for a second dose (after 2 h) and potentially a third dose for subsequent recurrence were patients randomised to either sumatriptan or placebo
Gobel 2000	No useable data - only 4 h efficacy data reported
Landy 2004 (Study 1)	High proportion of patients treated moderate or severe headache when protocol required treatment of headache when mild, therefore baseline pain intensity too heterogeneous to interpret results. Also discrepancies in reporting make number of patients analysed for a particular outcome un-interpretable.
Midelfart 1994	No useable data - only 4 h data reported and number of patients analysed for particular outcome un-interpretable
Padma 1998	Inadequate randomisation - alternating allocation
Pradel 2005	No useable data - no outcomes reported for individual study treatments
Rapoport 1995	First dose of subcutaneous sumatriptan not randomised, only for a second dose (after 4 h) and potentially a third dose for subsequent recurrence were patients randomised to either oral sumatriptan or placebo
Rederich 1995	No useable data - outcomes reported as % of patients experiencing outcome, but number of patients analysed for particular outcomes not reported
Salonen 1999	Only compares different doses of sumatriptan, no placebo or alternative active comparator
Savani 2001	One dose of sumatriptan compared against another with no placebo control, and baseline population enriched/selected for tolerance of adverse events and non-response to 50 mg sumatriptan
Scott 1996	First dose of sumatriptan not randomised, only for a second dose (after 4 h) and potentially a third dose for subsequent recurrence were patients randomised to either sumatriptan or placebo
Sramek 1999	No useable data - only pooled data for 3 different doses of sumatriptan reported
SUMA4014	First dose of sumatriptan is non-randomised and only single-blinded; only participants who fail to respond to the initial dose are given a subsequent randomised, double-blinded dose of sumatriptan (25 mg or 50 mg) or placebo
Tepper 2006	Only attacks meeting IHS criteria for probably migraine (2004 IHS) or migrainous disorder (1988 IHS) eligible
Tfelt-Hansen 2000	Data reported in Tfelt-Hansen 1995
Wells 2001	No useable data - efficacy data reported in Sandrini 2002
Wells 2003	No useable data - efficacy data reported in Sandrini 2002

GP: general practitioner; h: hour; IHS: International Headache Society

DATA AND ANALYSES

Comparison 1. Oral sumatriptan 25 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain-free at 2 h	3	1108	Risk Ratio (M-H, Fixed, 95% CI)	2.66 [1.79, 3.96]
2 Headache relief at 1 h	3	745	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [1.17, 2.29]
3 Headache relief at 2 h	5	1580	Risk Ratio (M-H, Fixed, 95% CI)	1.66 [1.43, 1.92]
4 Use of rescue medication	2	1282	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.48, 0.68]
4.1 Up to 4 h after initial dosing	2	1282	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.48, 0.68]
5 Relief of associated symptoms	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Relief of nausea at 2 h	4	550	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [1.18, 1.87]
5.2 Relief of photophobia at 2 h	3	411	Risk Ratio (M-H, Fixed, 95% CI)	1.82 [1.32, 2.53]
6 Relief of functional disability at 2 h	3	381	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [1.07, 1.77]
7 Any adverse event within 24 h	4	1550	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [1.00, 1.30]
8 Individual adverse events	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Malaise/fatigue/asthenia	3	1419	Risk Ratio (M-H, Fixed, 95% CI)	2.61 [1.17, 5.82]
8.2 Dizziness/vertigo	4	1550	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.61, 1.59]
8.3 Nausea/vomiting	4	1550	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.74, 1.75]
8.4 Mouth disorder/disturbance of taste	3	1148	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.49, 1.36]
8.5 Chest pain/symptoms	3	1419	Risk Ratio (M-H, Fixed, 95% CI)	1.75 [0.71, 4.33]
8.6 Paraesthesia/numbness	3	1148	Risk Ratio (M-H, Fixed, 95% CI)	3.40 [1.37, 8.43]
8.7 Headache	3	1148	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.67, 1.91]
8.8 Drowsiness/somnolence	3	1148	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.53, 1.55]
9 Any adverse event withdrawal	2	841	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.20, 7.26]
10 Headache relief at 2 h - effect of quality score	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 All studies	5	1580	Risk Ratio (M-H, Fixed, 95% CI)	1.66 [1.43, 1.92]
10.2 Only quality score ≥ 3	4	1449	Risk Ratio (M-H, Fixed, 95% CI)	1.63 [1.40, 1.90]

Analysis 1.1. Comparison 1 Oral sumatriptan 25 mg versus placebo, Outcome 1 Pain-free at 2 h.

Study or subgroup	Sumatriptan 25 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
160-104	29/180	8/93		29%	1.87[0.89,3.93]
Cutler 1995	14/66	5/65		13.85%	2.76[1.05,7.22]
Goldstein 1998	158/563	13/141		57.15%	3.04[1.78,5.19]
Total (95% CI)	**809**	**299**		**100%**	**2.66[1.79,3.96]**
Total events: 201 (Sumatriptan 25 mg), 26 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.11, df=2(P=0.57); I^2=0%					
Test for overall effect: Z=4.84(P<0.0001)					

Favours placebo — Favours sumatriptan

Analysis 1.2. Comparison 1 Oral sumatriptan 25 mg versus placebo, Outcome 2 Headache relief at 1 h.

Study or subgroup	Sumatriptan 25 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
160-104	42/180	20/93		53.68%	1.09[0.68,1.74]
Pfaffenrath 1998	83/286	13/91		40.15%	2.03[1.19,3.47]
Sargent 1995	12/48	3/47		6.17%	3.92[1.18,13]
Total (95% CI)	**514**	**231**		**100%**	**1.64[1.17,2.29]**
Total events: 137 (Sumatriptan 25 mg), 36 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=5.61, df=2(P=0.06); I^2=64.32%					
Test for overall effect: Z=2.89(P=0)					

Favours placebo — Favours sumatriptan

Analysis 1.3. Comparison 1 Oral sumatriptan 25 mg versus placebo, Outcome 3 Headache relief at 2 h.

Study or subgroup	Sumatriptan 25 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
160-104	90/180	34/93		22.71%	1.37[1.01,1.86]
Cutler 1995	34/66	17/65		8.68%	1.97[1.23,3.15]
Goldstein 1998	349/563	54/141		43.76%	1.62[1.3,2.02]
Pfaffenrath 1998	140/286	27/91		20.75%	1.65[1.18,2.31]
Sargent 1995	25/48	8/47		4.1%	3.06[1.54,6.08]

Favours placebo — Favours sumatriptan

Study or subgroup	Sumatriptan 25 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Total (95% CI)	**1143**	**437**	♦	**100%**	**1.66[1.43,1.92]**
Total events: 638 (Sumatriptan 25 mg), 140 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=5.15, df=4(P=0.27); I^2=22.28%					
Test for overall effect: Z=6.79(P<0.0001)					

Favours placebo 0.01 0.1 1 10 100 Favours sumatriptan

Analysis 1.4. Comparison 1 Oral sumatriptan 25 mg versus placebo, Outcome 4 Use of rescue medication.

Study or subgroup	Sumatriptan 25 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 Up to 4 h after initial dosing					
Goldstein 1998	141/563	63/141	■	47.27%	0.56[0.44,0.71]
Kolodny 2004	66/290	112/288	■	52.73%	0.59[0.45,0.76]
Subtotal (95% CI)	**853**	**429**	♦	**100%**	**0.57[0.48,0.68]**
Total events: 207 (Sumatriptan 25 mg), 175 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.06, df=1(P=0.8); I^2=0%					
Test for overall effect: Z=6.24(P<0.0001)					
Total (95% CI)	**853**	**429**	♦	**100%**	**0.57[0.48,0.68]**
Total events: 207 (Sumatriptan 25 mg), 175 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.06, df=1(P=0.8); I^2=0%					
Test for overall effect: Z=6.24(P<0.0001)					

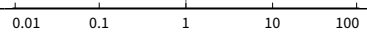
Favours sumatriptan 0.01 0.1 1 10 100 Favours placebo

Analysis 1.5. Comparison 1 Oral sumatriptan 25 mg versus placebo, Outcome 5 Relief of associated symptoms.

Study or subgroup	Sumatriptan 25 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.5.1 Relief of nausea at 2 h					
160-104	31/82	10/36	■	17.45%	1.36[0.75,2.47]
Cutler 1995	33/55	26/54	■	32.94%	1.25[0.88,1.77]
Pfaffenrath 1998	85/176	19/64	■	34.98%	1.63[1.08,2.44]
Sargent 1995	23/44	11/39	■	14.64%	1.85[1.04,3.29]
Subtotal (95% CI)	**357**	**193**	♦	**100%**	**1.49[1.18,1.87]**
Total events: 172 (Sumatriptan 25 mg), 66 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.81, df=3(P=0.61); I^2=0%					
Test for overall effect: Z=3.42(P=0)					
1.5.2 Relief of photophobia at 2 h					
160-104	59/129	19/63	■	61.12%	1.52[1,2.31]
Cutler 1995	25/64	10/61	■	24.51%	2.38[1.25,4.54]
Sargent 1995	13/47	6/47	■	14.36%	2.17[0.9,5.22]
Subtotal (95% CI)	**240**	**171**	♦	**100%**	**1.82[1.32,2.53]**

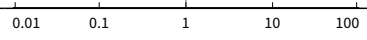
Favours placebo 0.01 0.1 1 10 100 Favours sumatriptan

Study or subgroup	Sumatriptan 25 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Total events: 97 (Sumatriptan 25 mg), 35 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.55, df=2(P=0.46); I^2=0%					
Test for overall effect: Z=3.61(P=0)					



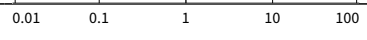
Analysis 1.6. Comparison 1 Oral sumatriptan 25 mg versus placebo, Outcome 6 Relief of functional disability at 2 h.

Study or subgroup	Sumatriptan 25 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
160-104	70/135	34/68		73.45%	1.04[0.78,1.38]
Cutler 1995	27/55	11/53		18.2%	2.37[1.31,4.27]
Sargent 1995	10/30	6/40		8.35%	2.22[0.91,5.44]
Total (95% CI)	**220**	**161**		**100%**	**1.38[1.07,1.77]**
Total events: 107 (Sumatriptan 25 mg), 51 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=8.05, df=2(P=0.02); I^2=75.15%					
Test for overall effect: Z=2.51(P=0.01)					



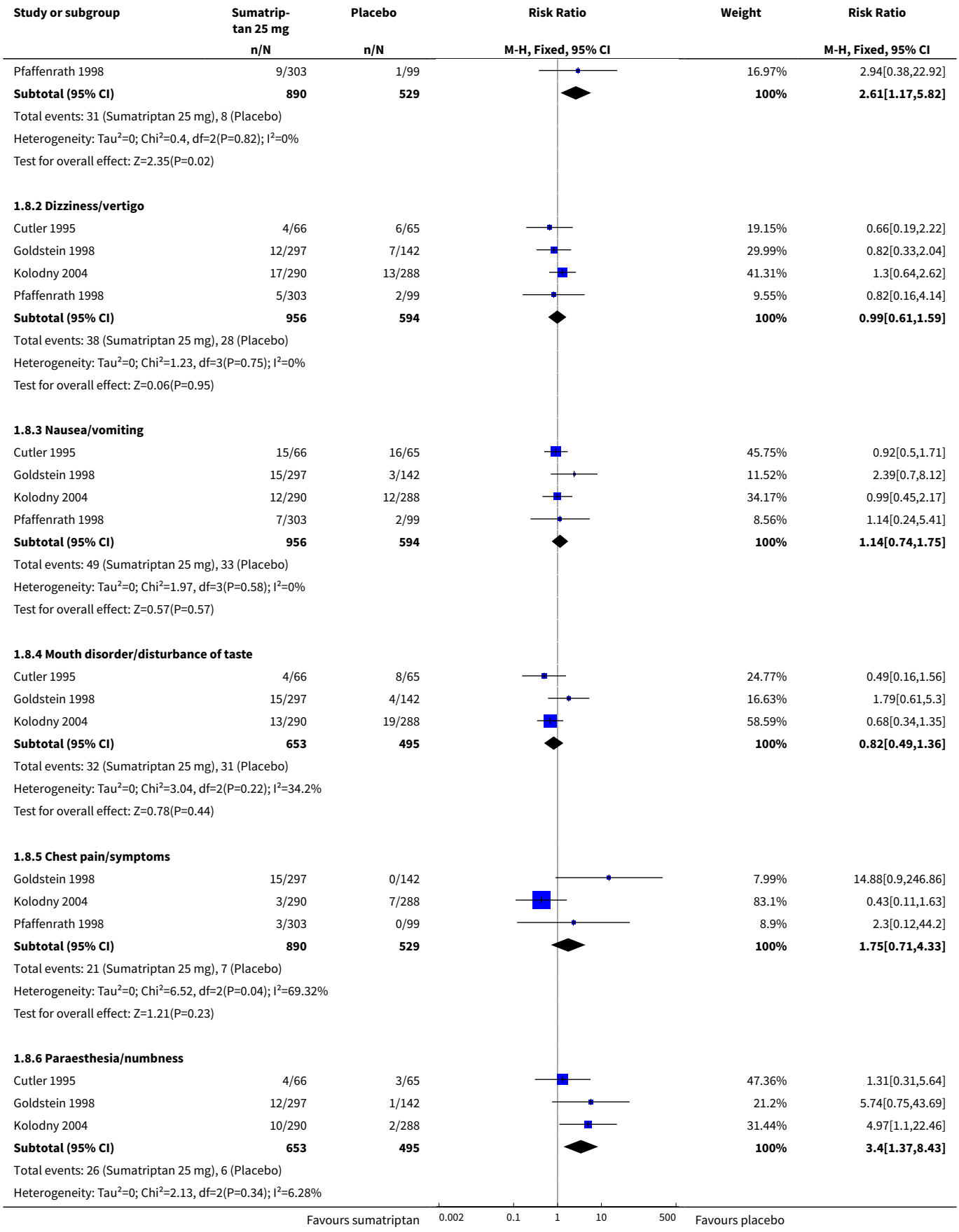
Analysis 1.7. Comparison 1 Oral sumatriptan 25 mg versus placebo, Outcome 7 Any adverse event within 24 h.

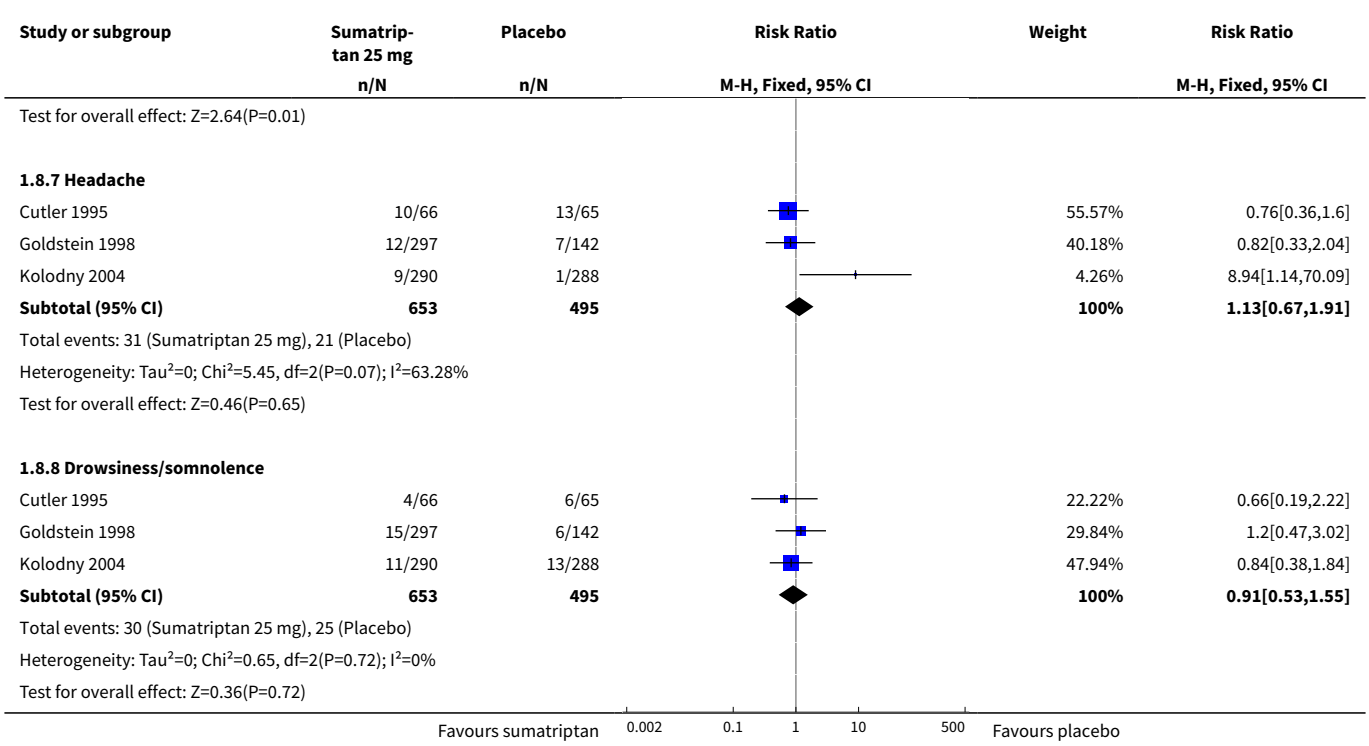
Study or subgroup	Sumatriptan 25 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Cutler 1995	47/66	48/65		19.46%	0.96[0.78,1.19]
Goldstein 1998	137/297	50/142		27.22%	1.31[1.02,1.69]
Kolodny 2004	113/290	102/288		41.18%	1.1[0.89,1.36]
Pfaffenrath 1998	74/303	20/99		12.13%	1.21[0.78,1.87]
Total (95% CI)	**956**	**594**		**100%**	**1.14[1,1.3]**
Total events: 371 (Sumatriptan 25 mg), 220 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=3.8, df=3(P=0.28); I^2=21.08%					
Test for overall effect: Z=2.01(P=0.04)					



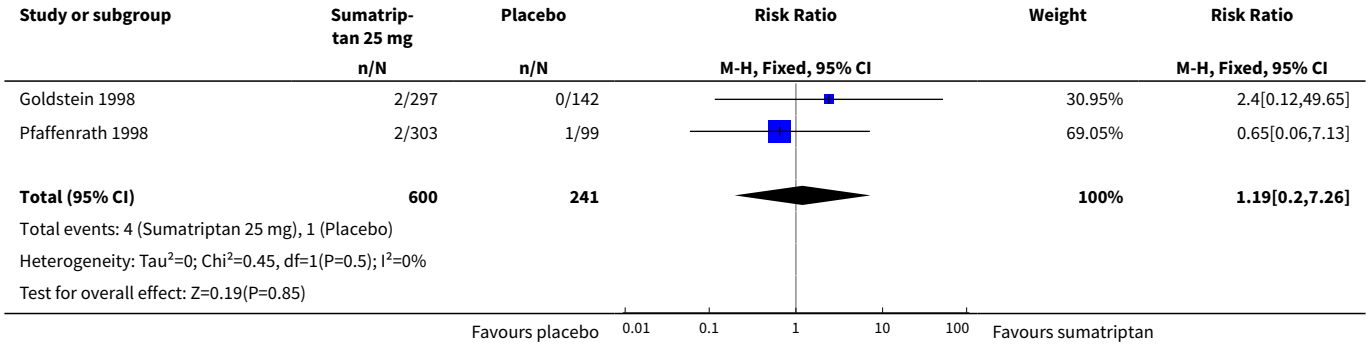
Analysis 1.8. Comparison 1 Oral sumatriptan 25 mg versus placebo, Outcome 8 Individual adverse events.

Study or subgroup	Sumatriptan 25 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.8.1 Malaise/fatigue/asthenia					
Goldstein 1998	9/297	1/142		15.24%	4.3[0.55,33.64]
Kolodny 2004	13/290	6/288		67.79%	2.15[0.83,5.58]

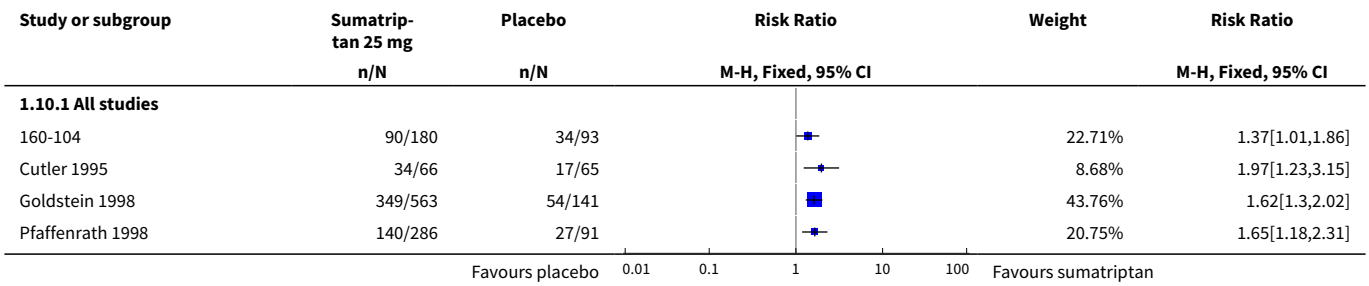


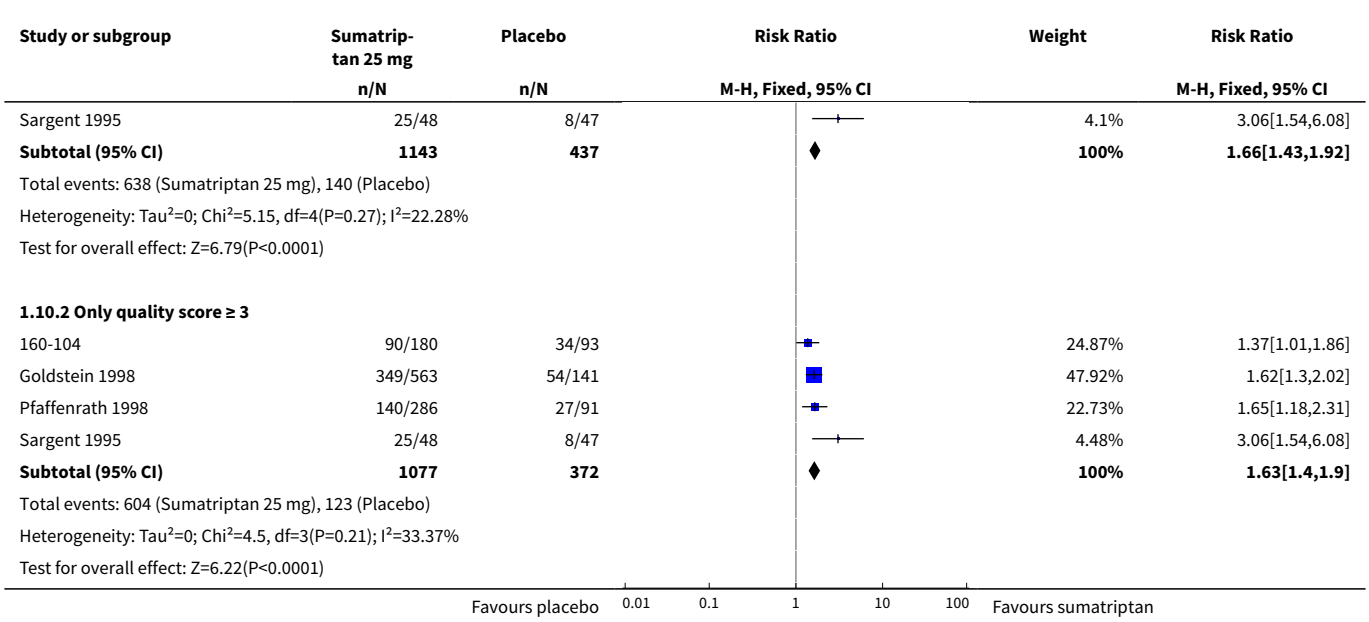


Analysis 1.9. Comparison 1 Oral sumatriptan 25 mg versus placebo, Outcome 9 Any adverse event withdrawal.



Analysis 1.10. Comparison 1 Oral sumatriptan 25 mg versus placebo, Outcome 10 Headache relief at 2 h - effect of quality score.





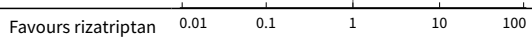
Comparison 2. Oral sumatriptan 25 mg versus rizatriptan 5 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain free at 2 h	2	2210	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.74, 0.95]
2 Headache relief at 1 h	2	2210	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.81, 1.02]
3 Headache relief at 2 h	2	2210	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.84, 0.95]
4 Use of rescue medication	2	1698	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.82, 1.14]
4.1 Up to 4 h after initial dosing	2	1698	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.82, 1.14]
5 Any adverse event within 24 h	2	1169	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.91, 1.19]
6 Individual adverse events	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Paraesthesia	2	1169	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [0.76, 2.77]
6.2 Chest symptoms	2	1169	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.64, 2.53]
6.3 Dizziness/vertigo	2	1169	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.41, 1.00]
6.4 Somnolence	2	1169	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.53, 1.49]
6.5 Nausea/vomiting	2	1169	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.63, 1.82]
6.6 Dry mouth/mouth disorder	2	1169	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.53, 1.42]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.7 Malaise/fatigue/asthenia	2	1169	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.47, 1.40]

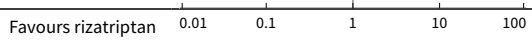
Analysis 2.1. Comparison 2 Oral sumatriptan 25 mg versus rizatriptan 5 mg, Outcome 1 Pain free at 2 h.

Study or subgroup	Sumatriptan 25 mg n/N	Rizatriptan 5 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Goldstein 1998	158/563	184/557		50.41%	0.85[0.71,1.01]
Kolodny 2004	152/554	179/536		49.59%	0.82[0.69,0.98]
Total (95% CI)	**1117**	**1093**		**100%**	**0.84[0.74,0.95]**
Total events: 310 (Sumatriptan 25 mg), 363 (Rizatriptan 5 mg)					
Heterogeneity: Tau^2=0; Chi^2=0.07, df=1(P=0.8); I^2=0%					
Test for overall effect: Z=2.78(P=0.01)					



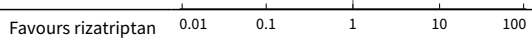
Analysis 2.2. Comparison 2 Oral sumatriptan 25 mg versus rizatriptan 5 mg, Outcome 2 Headache relief at 1 h.

Study or subgroup	Sumatriptan 25 mg n/N	Rizatriptan 5 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Goldstein 1998	194/563	209/557		51.46%	0.92[0.79,1.07]
Kolodny 2004	181/554	195/536		48.54%	0.9[0.76,1.06]
Total (95% CI)	**1117**	**1093**		**100%**	**0.91[0.81,1.02]**
Total events: 375 (Sumatriptan 25 mg), 404 (Rizatriptan 5 mg)					
Heterogeneity: Tau^2=0; Chi^2=0.04, df=1(P=0.85); I^2=0%					
Test for overall effect: Z=1.66(P=0.1)					

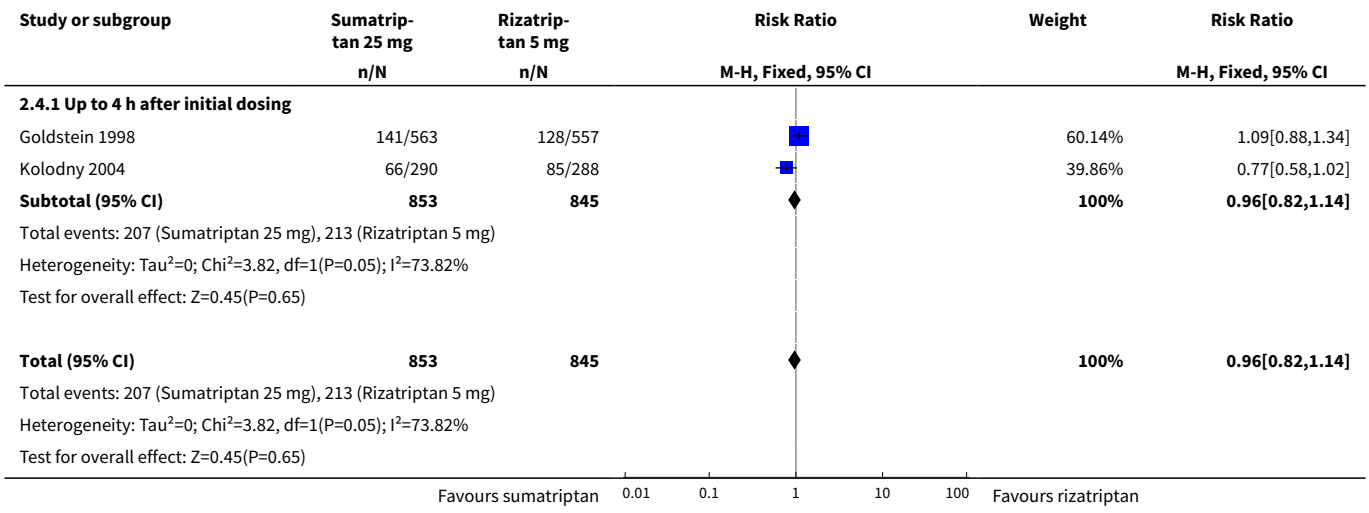


Analysis 2.3. Comparison 2 Oral sumatriptan 25 mg versus rizatriptan 5 mg, Outcome 3 Headache relief at 2 h.

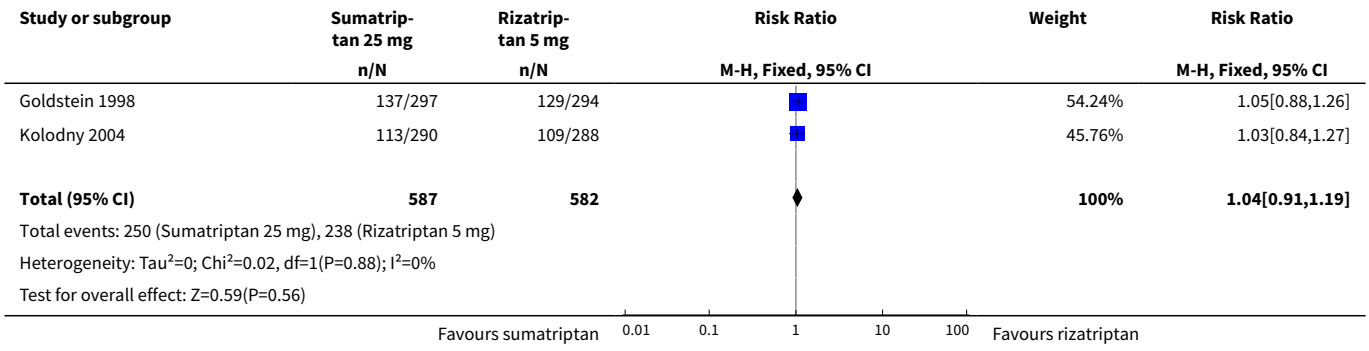
Study or subgroup	Sumatriptan 25 mg n/N	Rizatriptan 5 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Goldstein 1998	349/563	379/557		51.57%	0.91[0.84,0.99]
Kolodny 2004	320/554	352/536		48.43%	0.88[0.8,0.97]
Total (95% CI)	**1117**	**1093**		**100%**	**0.9[0.84,0.95]**
Total events: 669 (Sumatriptan 25 mg), 731 (Rizatriptan 5 mg)					
Heterogeneity: Tau^2=0; Chi^2=0.29, df=1(P=0.59); I^2=0%					
Test for overall effect: Z=3.39(P=0)					



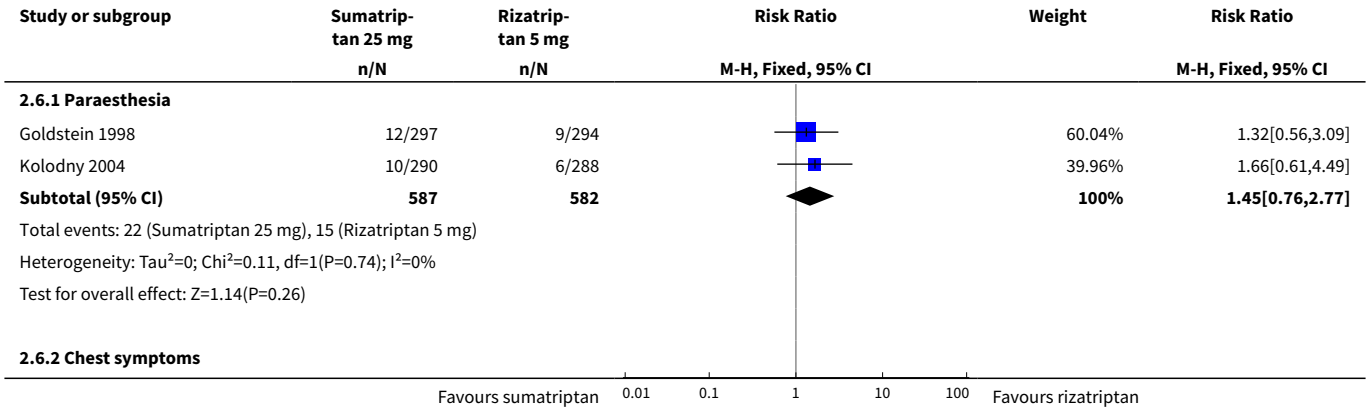
Analysis 2.4. Comparison 2 Oral sumatriptan 25 mg versus rizatriptan 5 mg, Outcome 4 Use of rescue medication.

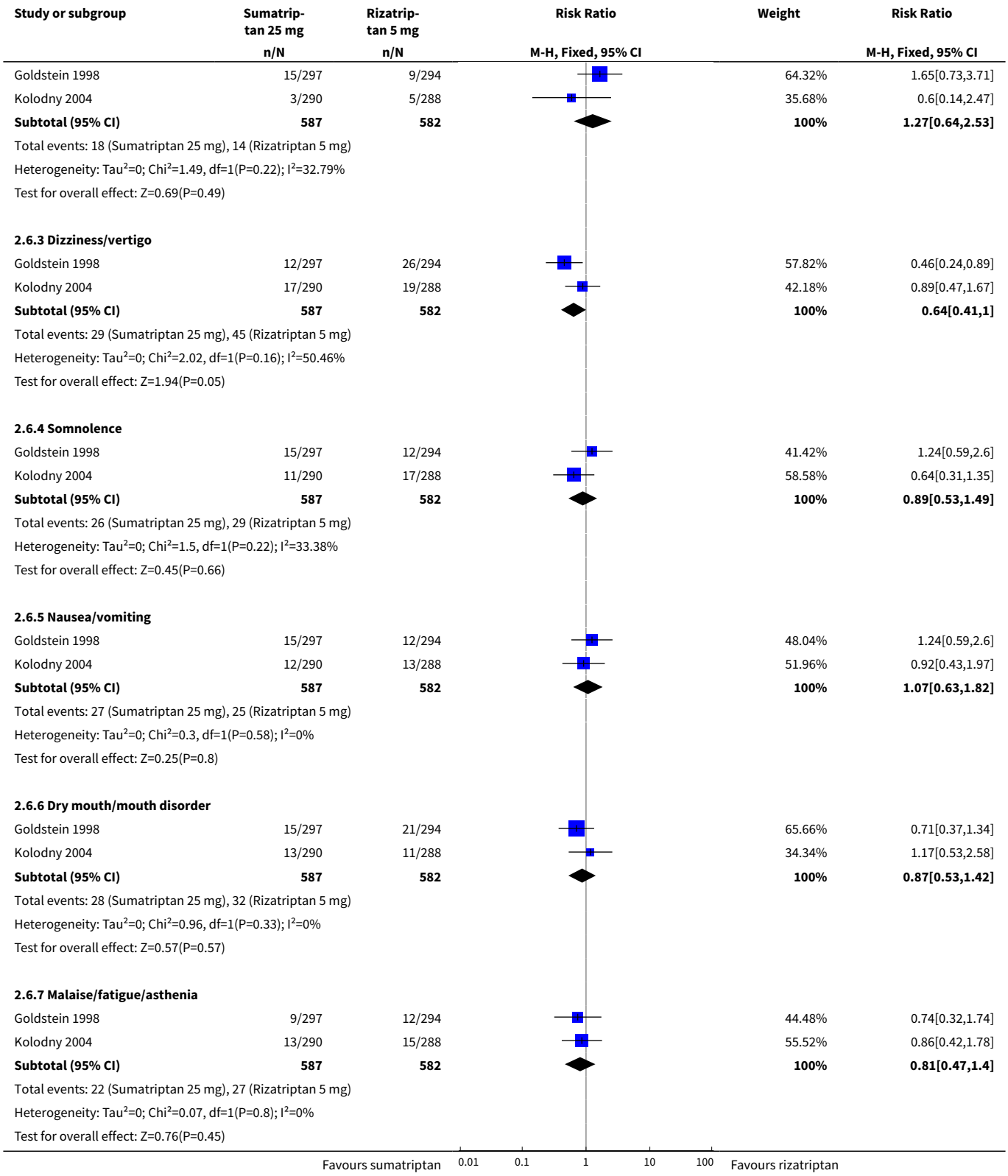


Analysis 2.5. Comparison 2 Oral sumatriptan 25 mg versus rizatriptan 5 mg, Outcome 5 Any adverse event within 24 h.



Analysis 2.6. Comparison 2 Oral sumatriptan 25 mg versus rizatriptan 5 mg, Outcome 6 Individual adverse events.



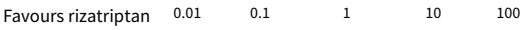


Comparison 3. Oral sumatriptan 25 mg versus rizatriptan 10 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain-free at 2 h	2	2231	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.62, 0.79]
2 Headache relief at 1 h	2	2231	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.74, 0.91]
3 Headache relief at 2 h	2	2231	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.80, 0.91]
4 Use of rescue medication	2	1716	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [1.00, 1.43]
4.1 Up to 4 h after initial dosing	2	1716	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [1.00, 1.43]
5 Any adverse event within 24 h	2	1186	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.81, 1.05]
6 Individual adverse events	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Paraesthesia	2	1186	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.46, 1.39]
6.2 Chest symptoms	2	1186	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.59, 2.23]
6.3 Dizziness/vertigo	2	1186	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.33, 0.77]
6.4 Somnolence	2	1186	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.38, 0.97]
6.5 Nausea/vomiting	2	1186	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.52, 1.42]
6.6 Dry mouth/mouth disorder	2	1186	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.53, 1.41]
6.7 Malaise/fatigue/asthenia	2	1186	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.62, 2.03]

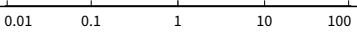
Analysis 3.1. Comparison 3 Oral sumatriptan 25 mg versus rizatriptan 10 mg, Outcome 1 Pain-free at 2 h.

Study or subgroup	Sumatriptan 25 mg n/N	Rizatriptan 10 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Goldstein 1998	158/563	232/567		52.48%	0.69[0.58,0.81]
Kolodny 2004	152/554	208/547		47.52%	0.72[0.61,0.86]
Total (95% CI)	**1117**	**1114**		**100%**	**0.7[0.62,0.79]**
Total events: 310 (Sumatriptan 25 mg), 440 (Rizatriptan 10 mg)					
Heterogeneity: Tau^2=0; Chi^2=0.17, df=1(P=0.68); I^2=0%					
Test for overall effect: Z=5.79(P<0.0001)					



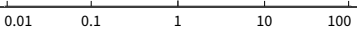
Analysis 3.2. Comparison 3 Oral sumatriptan 25 mg versus rizatriptan 10 mg, Outcome 2 Headache relief at 1 h.

Study or subgroup	Sumatriptan 25 mg n/N	Rizatriptan 10 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Goldstein 1998	194/563	236/567		51.51%	0.83[0.71,0.96]
Kolodny 2004	181/554	220/547		48.49%	0.81[0.69,0.95]
Total (95% CI)	**1117**	**1114**		**100%**	**0.82[0.74,0.91]**
Total events: 375 (Sumatriptan 25 mg), 456 (Rizatriptan 10 mg)					
Heterogeneity: Tau^2=0; Chi^2=0.03, df=1(P=0.86); I^2=0%					
Test for overall effect: Z=3.58(P=0)					



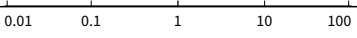
Analysis 3.3. Comparison 3 Oral sumatriptan 25 mg versus rizatriptan 10 mg, Outcome 3 Headache relief at 2 h.

Study or subgroup	Sumatriptan 25 mg n/N	Rizatriptan 10 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Goldstein 1998	349/563	408/567		52.06%	0.86[0.79,0.94]
Kolodny 2004	320/554	372/547		47.94%	0.85[0.78,0.93]
Total (95% CI)	**1117**	**1114**		**100%**	**0.86[0.8,0.91]**
Total events: 669 (Sumatriptan 25 mg), 780 (Rizatriptan 10 mg)					
Heterogeneity: Tau^2=0; Chi^2=0.05, df=1(P=0.82); I^2=0%					
Test for overall effect: Z=4.97(P<0.0001)					

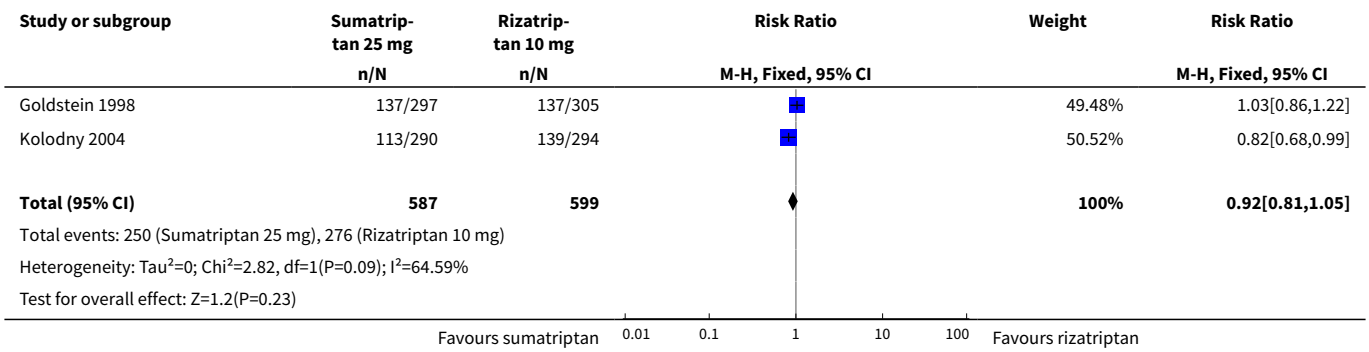


Analysis 3.4. Comparison 3 Oral sumatriptan 25 mg versus rizatriptan 10 mg, Outcome 4 Use of rescue medication.

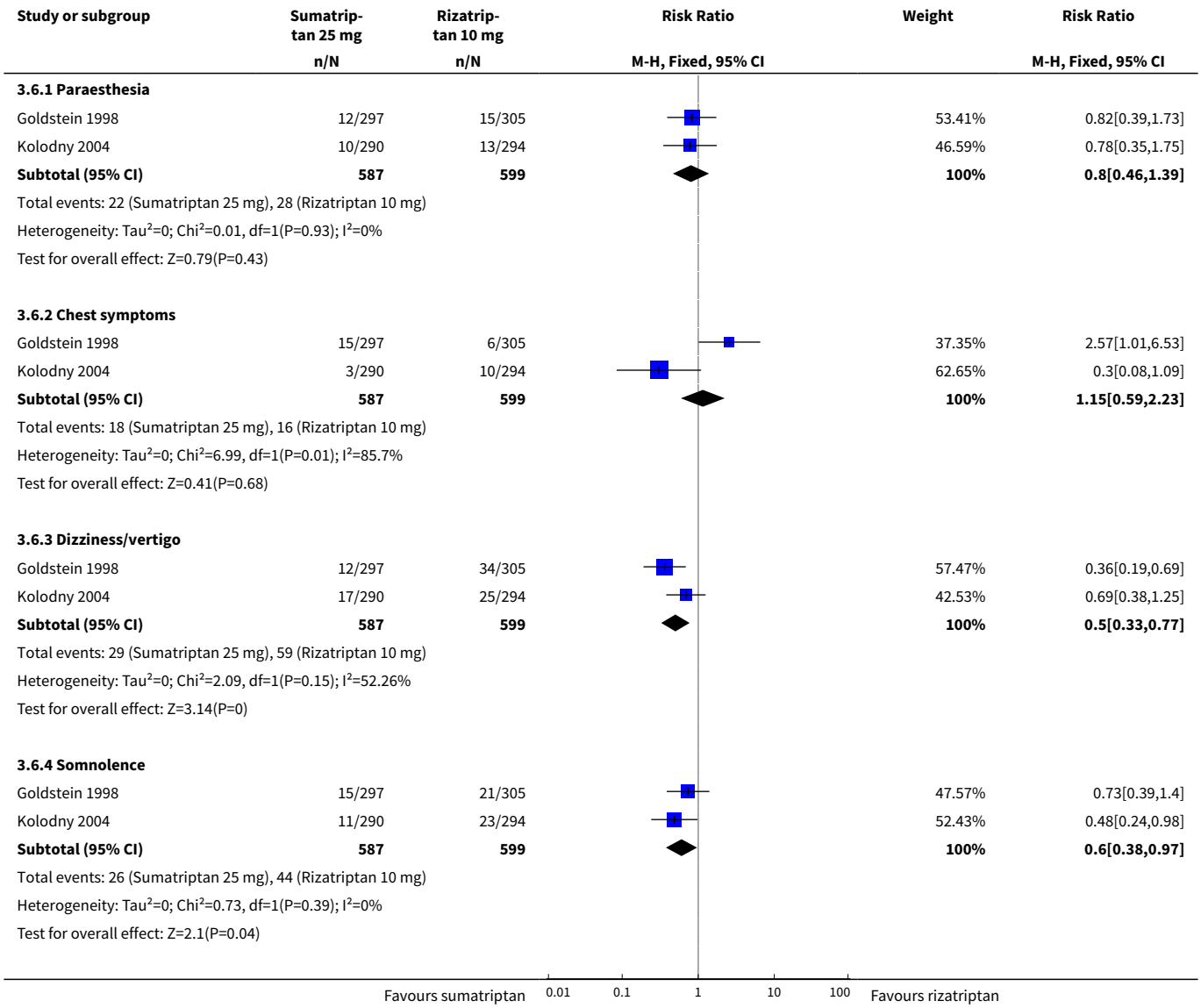
Study or subgroup	Sumatriptan 25 mg n/N	Rizatriptan 10 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.4.1 Up to 4 h after initial dosing					
Goldstein 1998	141/563	108/567		61.87%	1.31[1.05,1.64]
Kolodny 2004	66/290	67/296		38.13%	1.01[0.75,1.36]
Subtotal (95% CI)	**853**	**863**		**100%**	**1.2[1,1.43]**
Total events: 207 (Sumatriptan 25 mg), 175 (Rizatriptan 10 mg)					
Heterogeneity: Tau^2=0; Chi^2=2, df=1(P=0.16); I^2=49.9%					
Test for overall effect: Z=1.98(P=0.05)					
Total (95% CI)	**853**	**863**		**100%**	**1.2[1,1.43]**
Total events: 207 (Sumatriptan 25 mg), 175 (Rizatriptan 10 mg)					
Heterogeneity: Tau^2=0; Chi^2=2, df=1(P=0.16); I^2=49.9%					
Test for overall effect: Z=1.98(P=0.05)					

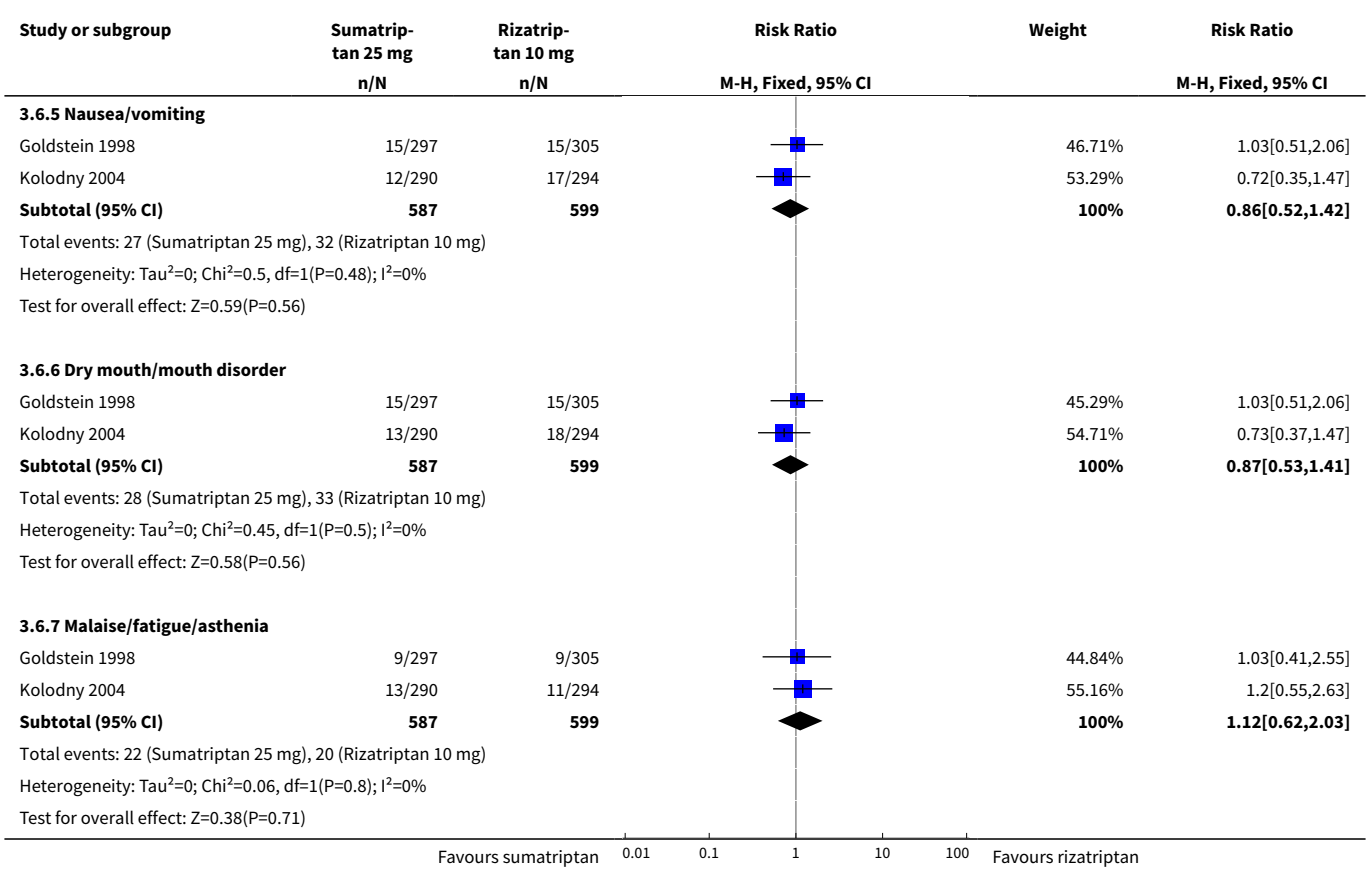


Analysis 3.5. Comparison 3 Oral sumatriptan 25 mg versus rizatriptan 10 mg, Outcome 5 Any adverse event within 24 h.



Analysis 3.6. Comparison 3 Oral sumatriptan 25 mg versus rizatriptan 10 mg, Outcome 6 Individual adverse events.





Comparison 4. Oral sumatriptan 50 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain-free at 2 h	18		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Moderate or severe baseline pain intensity	12	6447	Risk Ratio (M-H, Fixed, 95% CI)	2.70 [2.38, 3.06]
1.2 Mild baseline pain intensity	6	1514	Risk Ratio (M-H, Fixed, 95% CI)	2.03 [1.74, 2.37]
2 Pain free at 1 h	9		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Moderate or severe baseline pain intensity	5	1735	Risk Ratio (M-H, Fixed, 95% CI)	2.64 [1.49, 4.67]
2.2 Mild baseline pain intensity	4	1246	Risk Ratio (M-H, Fixed, 95% CI)	1.87 [1.48, 2.37]
3 Headache relief at 1 h	9	2766	Risk Ratio (M-H, Fixed, 95% CI)	1.80 [1.52, 2.13]
4 Headache relief at 2 h	18	8102	Risk Ratio (M-H, Fixed, 95% CI)	1.80 [1.70, 1.91]
5 24 h sustained pain-free	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Moderate or severe baseline pain intensity	3	2526	Risk Ratio (M-H, Fixed, 95% CI)	2.63 [2.07, 3.35]
5.2 Mild baseline pain intensity	4	866	Risk Ratio (M-H, Fixed, 95% CI)	2.81 [2.05, 3.86]
6 24 h sustained headache relief	3	2526	Risk Ratio (M-H, Fixed, 95% CI)	1.91 [1.66, 2.20]
7 Use of rescue medication	11		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Up to 24 h after initial dosing in participants with moderate or severe baseline pain	4	2079	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.68, 0.87]
7.2 Up to 24 h after initial dosing in participants with mild baseline pain	2	384	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.42, 0.68]
7.3 Up to 4 h after initial dosing	5	2098	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.50, 0.64]
8 Relief of associated symptoms in participants with moderate or severe baseline pain intensity	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Relief of nausea at 2 h	7	973	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [1.16, 1.65]
8.2 Relief of photophobia at 2 h	6	1144	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [1.22, 1.65]
8.3 Relief of phonophobia at 2 h	4	852	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [1.16, 1.60]
8.4 Relief of photophobia or phonophobia at 2 h	2	440	Risk Ratio (M-H, Fixed, 95% CI)	2.06 [1.55, 2.75]
9 Relief of associated symptoms in participants with mild baseline pain intensity	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 Relief of nausea at 2 h	2	280	Risk Ratio (M-H, Fixed, 95% CI)	6.88 [3.78, 12.51]
9.2 Relief of photophobia at 2 h	2	483	Risk Ratio (M-H, Fixed, 95% CI)	2.95 [2.20, 3.97]
9.3 Relief of phonophobia at 2 h	2	413	Risk Ratio (M-H, Fixed, 95% CI)	2.99 [2.15, 4.16]
10 Relief of functional disability at 2 h	4	607	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [1.17, 1.79]
11 Any adverse event within 24 h	15		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 Moderate or severe baseline pain intensity	10	3728	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [1.17, 1.44]
11.2 Mild baseline pain intensity	5	1242	Risk Ratio (M-H, Fixed, 95% CI)	2.26 [1.62, 3.16]
12 Individual adverse events	13		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 Malaise/fatigue/asthenia	10	3689	Risk Ratio (M-H, Fixed, 95% CI)	2.68 [1.59, 4.50]

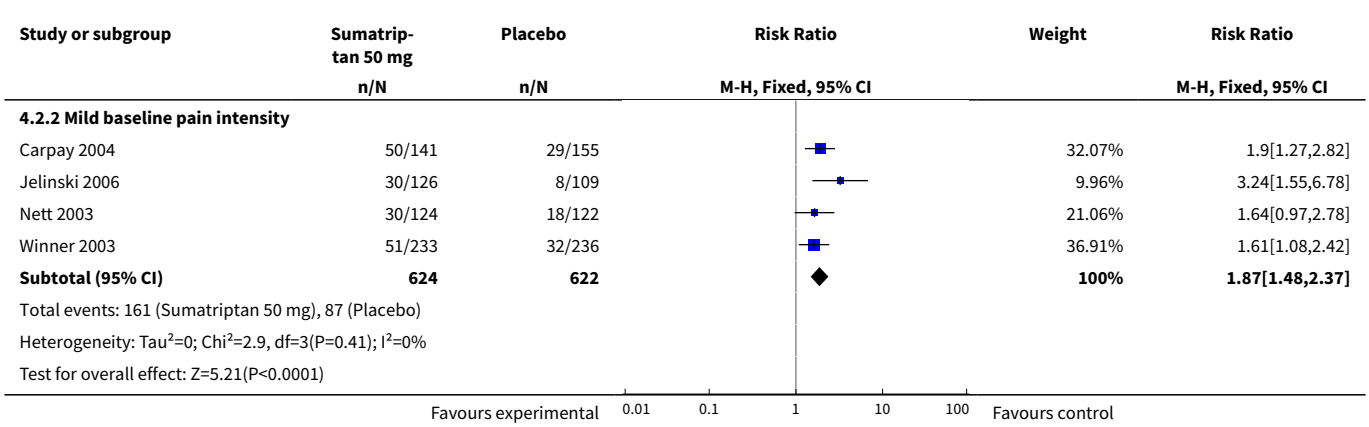
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.2 Dizziness/vertigo	12	4211	Risk Ratio (M-H, Fixed, 95% CI)	1.78 [1.28, 2.47]
12.3 Nausea/vomiting	12	3799	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [0.97, 1.96]
12.4 Mouth disorder/disturbance of taste	5	1887	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [0.90, 2.13]
12.5 Chest pain/symptoms	7	2673	Risk Ratio (M-H, Fixed, 95% CI)	2.11 [1.14, 3.92]
12.6 Heat sensations/flushing	4	1515	Risk Ratio (M-H, Fixed, 95% CI)	3.83 [1.53, 9.59]
12.7 Diarrhoea	3	1327	Risk Ratio (M-H, Fixed, 95% CI)	2.51 [1.19, 5.30]
12.8 Feeling of heaviness/tightness	4	1179	Risk Ratio (M-H, Fixed, 95% CI)	3.03 [0.88, 10.43]
12.9 Paraesthesia/numbness	9	3098	Risk Ratio (M-H, Fixed, 95% CI)	2.65 [1.41, 5.00]
12.10 Headache	5	1904	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.81, 2.06]
12.11 Drowsiness/somnolence	8	2628	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.87, 2.09]
12.12 Anxiety	2	518	Risk Ratio (M-H, Fixed, 95% CI)	1.89 [0.36, 9.94]
12.13 Neck/back pain	2	364	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.09, 2.68]
13 Any adverse event withdrawal	4	1553	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.18, 7.08]
14 Pain free at 2 h - effect of quality score	12		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 Quality score ≥ 3	10	5835	Risk Ratio (M-H, Fixed, 95% CI)	2.64 [2.32, 2.99]
14.2 Quality score = 2	2	612	Risk Ratio (M-H, Fixed, 95% CI)	4.29 [2.19, 8.43]
15 Headache relief at 1 h - effect of quality score	9		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1 All studies	9	2766	Risk Ratio (M-H, Fixed, 95% CI)	1.80 [1.52, 2.13]
15.2 Only quality score ≥ 3	8	2281	Risk Ratio (M-H, Fixed, 95% CI)	1.92 [1.59, 2.31]
16 Headache relief at 2 h - effect of quality score	18		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 Quality score ≥ 3	14	6842	Risk Ratio (M-H, Fixed, 95% CI)	1.75 [1.65, 1.86]
16.2 Quality score = 2	4	1260	Risk Ratio (M-H, Fixed, 95% CI)	2.31 [1.87, 2.84]

Analysis 4.1. Comparison 4 Oral sumatriptan 50 mg versus placebo, Outcome 1 Pain-free at 2 h.

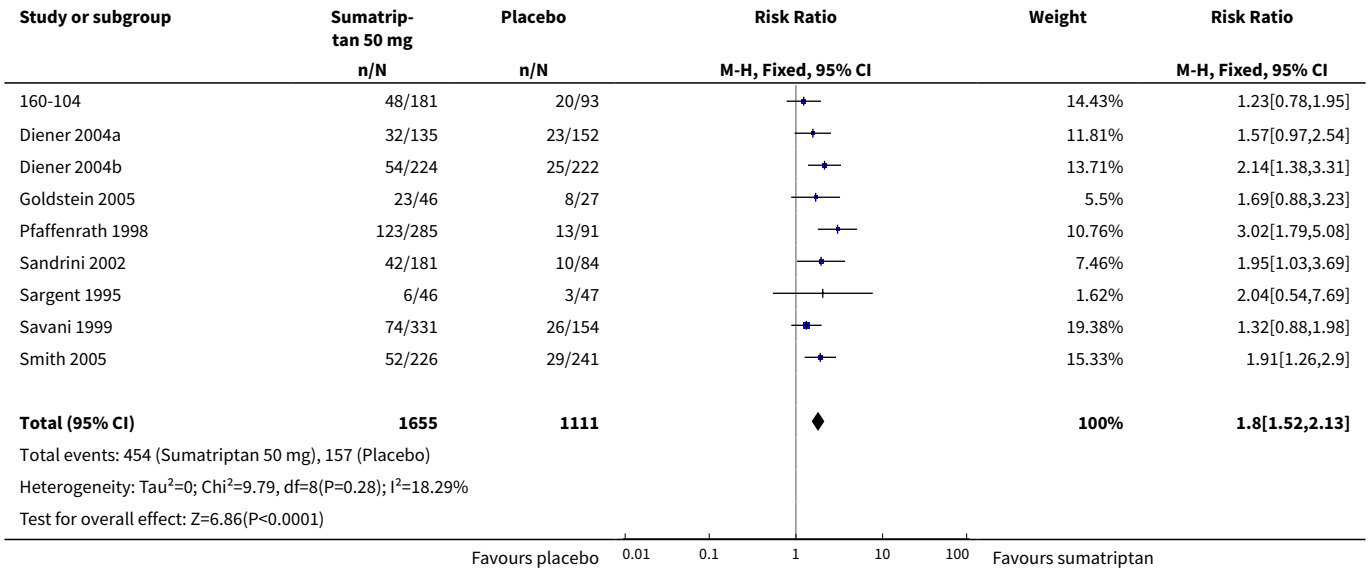
Study or subgroup	Sumatriptan 50 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.1.1 Moderate or severe baseline pain intensity					
160-104	31/181	8/93		3.48%	1.99[0.95,4.16]
Cutler 1995	10/62	5/65		1.61%	2.1[0.76,5.79]
Dahlof 2009	32/136	8/134		2.65%	3.94[1.89,8.24]
Diener 2004a	33/135	22/152		6.81%	1.69[1.04,2.75]
Diener 2004b	83/224	28/222		9.25%	2.94[2,4.32]
Goldstein 1998	209/566	13/141		6.84%	4.01[2.36,6.8]
Ishkanian 2007	26/108	22/107		7.27%	1.17[0.71,1.93]
Lipton 2000	157/870	17/240		8.76%	2.55[1.58,4.12]
Sandrini 2002	33/181	3/84		1.35%	5.1[1.61,16.17]
Savani 1999	63/331	5/154		2.24%	5.86[2.41,14.28]
Sheftell 2005	358/902	137/892		45.3%	2.58[2.17,3.07]
Smith 2005	45/226	14/241		4.46%	3.43[1.94,6.07]
Subtotal (95% CI)	**3922**	**2525**		**100%**	**2.7[2.38,3.06]**
Total events: 1080 (Sumatriptan 50 mg), 282 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=23.53, df=11(P=0.01); I^2=53.25%					
Test for overall effect: Z=15.59(P<0.0001)					
4.1.2 Mild baseline pain intensity					
Carpay 2004	70/141	30/155		16.77%	2.57[1.79,3.68]
Jelinski 2006	51/126	17/109		10.69%	2.6[1.6,4.22]
Nett 2003	62/124	35/122		20.7%	1.74[1.25,2.43]
Pini 1999	36/106	9/61		6.7%	2.3[1.19,4.45]
Tfelt-Hansen 2006	20/53	8/48		4.93%	2.26[1.1,4.66]
Winner 2003	118/233	69/236		40.22%	1.73[1.37,2.19]
Subtotal (95% CI)	**783**	**731**		**100%**	**2.03[1.74,2.37]**
Total events: 357 (Sumatriptan 50 mg), 168 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=5.38, df=5(P=0.37); I^2=7.09%					
Test for overall effect: Z=9.08(P<0.0001)					

Analysis 4.2. Comparison 4 Oral sumatriptan 50 mg versus placebo, Outcome 2 Pain free at 1 h.

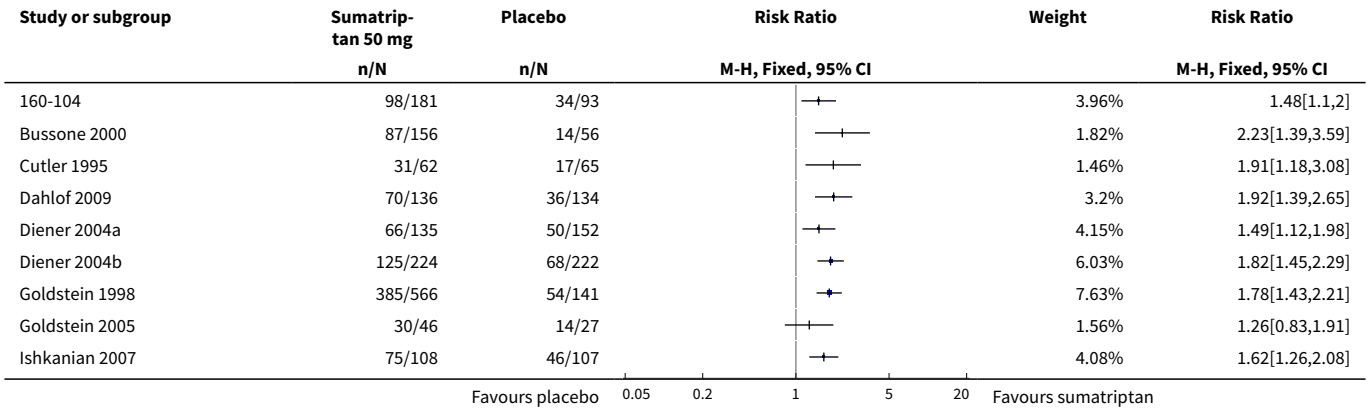
Study or subgroup	Sumatriptan 50 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.2.1 Moderate or severe baseline pain intensity					
Dahlof 2009	8/136	1/134		6.28%	7.88[1,62.16]
Diener 2004a	7/135	5/152		29.32%	1.58[0.51,4.85]
Diener 2004b	12/224	7/222		43.82%	1.7[0.68,4.24]
Sandrini 2002	9/181	1/84		8.51%	4.18[0.54,32.44]
Smith 2005	9/226	2/241		12.06%	4.8[1.05,21.97]
Subtotal (95% CI)	**902**	**833**		**100%**	**2.64[1.49,4.67]**
Total events: 45 (Sumatriptan 50 mg), 16 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=3.56, df=4(P=0.47); I^2=0%					
Test for overall effect: Z=3.32(P=0)					



Analysis 4.3. Comparison 4 Oral sumatriptan 50 mg versus placebo, Outcome 3 Headache relief at 1 h.



Analysis 4.4. Comparison 4 Oral sumatriptan 50 mg versus placebo, Outcome 4 Headache relief at 2 h.



Study or subgroup	Sumatriptan 50 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Kudrow 2005	60/144	42/141		3.75%	1.4[1.02,1.92]
Lines 2001	239/356	18/80		2.59%	2.98[1.97,4.51]
Lipton 2000	409/870	82/420		9.76%	2.41[1.96,2.96]
Pfaffenrath 1998	180/285	27/91		3.61%	2.13[1.53,2.96]
Sandrini 2002	88/181	25/84		3.01%	1.63[1.14,2.34]
Sargent 1995	25/46	8/47		0.7%	3.19[1.61,6.33]
Savani 1999	140/331	32/154		3.85%	2.04[1.46,2.84]
Sheftell 2005	603/902	375/892		33.28%	1.59[1.45,1.74]
Smith 2005	111/226	65/241		5.55%	1.82[1.42,2.33]
Total (95% CI)	**4955**	**3147**		**100%**	**1.8[1.7,1.91]**
Total events: 2822 (Sumatriptan 50 mg), 1007 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=35.64, df=17(P=0.01); I^2=52.3%					
Test for overall effect: Z=19.83(P<0.0001)					

Favours placebo 0.05 0.2 1 5 20 Favours sumatriptan

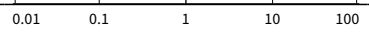
Analysis 4.5. Comparison 4 Oral sumatriptan 50 mg versus placebo, Outcome 5 24 h sustained pain-free.

Study or subgroup	Sumatriptan 50 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.5.1 Moderate or severe baseline pain intensity					
Sandrini 2002	20/181	3/84		4.93%	3.09[0.95,10.13]
Sheftell 2005	181/902	67/892		81.09%	2.67[2.05,3.48]
Smith 2005	25/226	12/241		13.98%	2.22[1.14,4.32]
Subtotal (95% CI)	**1309**	**1217**		**100%**	**2.63[2.07,3.35]**
Total events: 226 (Sumatriptan 50 mg), 82 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.33, df=2(P=0.85); I^2=0%					
Test for overall effect: Z=7.86(P<0.0001)					
4.5.2 Mild baseline pain intensity					
Carpay 2004	44/141	15/155		32.55%	3.22[1.88,5.53]
Jelinski 2006	30/126	7/109		17.1%	3.71[1.7,8.1]
Nett 2003	35/116	17/118		38.39%	2.09[1.25,3.52]
Tfelt-Hansen 2006	15/53	5/48		11.95%	2.72[1.07,6.91]
Subtotal (95% CI)	**436**	**430**		**100%**	**2.81[2.05,3.86]**
Total events: 124 (Sumatriptan 50 mg), 44 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.97, df=3(P=0.58); I^2=0%					
Test for overall effect: Z=6.39(P<0.0001)					

Favours placebo 0.05 0.2 1 5 20 Favours sumatriptan

Analysis 4.6. Comparison 4 Oral sumatriptan 50 mg versus placebo, Outcome 6 24 h sustained headache relief.

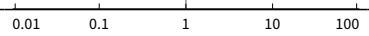
Study or subgroup	Sumatriptan 50 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Sandrini 2002	61/181	18/84		10.87%	1.57[1,2.49]
Sheftell 2005	327/902	161/892		71.58%	2.01[1.7,2.37]
Smith 2005	66/226	41/241		17.55%	1.72[1.22,2.42]
Total (95% CI)	**1309**	**1217**		**100%**	**1.91[1.66,2.2]**
Total events: 454 (Sumatriptan 50 mg), 220 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.42, df=2(P=0.49); I^2=0%					
Test for overall effect: Z=8.99(P<0.0001)					



Favours placebo — Favours sumatriptan

Analysis 4.7. Comparison 4 Oral sumatriptan 50 mg versus placebo, Outcome 7 Use of rescue medication.

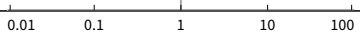
Study or subgroup	Sumatriptan 50 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.7.1 Up to 24 h after initial dosing in participants with moderate or severe baseline pain					
Diener 2004a	53/135	98/152		29.73%	0.61[0.48,0.77]
Ishkanian 2007	37/108	46/107		14.9%	0.8[0.57,1.12]
Lipton 2000	61/870	20/240		10.11%	0.84[0.52,1.37]
Smith 2005	115/226	145/241		45.26%	0.85[0.72,1]
Subtotal (95% CI)	**1339**	**740**		**100%**	**0.77[0.68,0.87]**
Total events: 266 (Sumatriptan 50 mg), 309 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=5.08, df=3(P=0.17); I^2=40.93%					
Test for overall effect: Z=4.17(P<0.0001)					
4.7.2 Up to 24 h after initial dosing in participants with mild baseline pain					
Jelinski 2006	44/126	68/109		68.74%	0.56[0.42,0.74]
Pini 1999	22/95	26/54		31.26%	0.48[0.3,0.76]
Subtotal (95% CI)	**221**	**163**		**100%**	**0.54[0.42,0.68]**
Total events: 66 (Sumatriptan 50 mg), 94 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.31, df=1(P=0.58); I^2=0%					
Test for overall effect: Z=5.13(P<0.0001)					
4.7.3 Up to 4 h after initial dosing					
Dahlof 2009	29/136	39/134		9.68%	0.73[0.48,1.11]
Diener 2004b	92/224	147/222		36.39%	0.62[0.52,0.74]
Goldstein 1998	108/566	63/141		24.86%	0.43[0.33,0.55]
Goldstein 2005	8/67	5/35		1.62%	0.84[0.3,2.36]
Kolodny 2004	59/285	112/288		27.46%	0.53[0.41,0.7]
Subtotal (95% CI)	**1278**	**820**		**100%**	**0.56[0.5,0.64]**
Total events: 296 (Sumatriptan 50 mg), 366 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=8.02, df=4(P=0.09); I^2=50.13%					
Test for overall effect: Z=9.05(P<0.0001)					



Favours sumatriptan — Favours placebo

Analysis 4.8. Comparison 4 Oral sumatriptan 50 mg versus placebo, Outcome 8 Relief of associated symptoms in participants with moderate or severe baseline pain intensity.

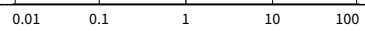
Study or subgroup	Sumatriptan 50 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.8.1 Relief of nausea at 2 h					
160-104	27/74	10/36		9.68%	1.31[0.72,2.41]
Cutler 1995	23/43	26/54		16.58%	1.11[0.75,1.65]
Ishkanian 2007	15/34	18/30		13.75%	0.74[0.46,1.19]
Kudrow 2005	32/95	24/97		17.08%	1.36[0.87,2.13]
Pfaffenrath 1998	106/197	19/64		20.63%	1.81[1.22,2.7]
Sandrini 2002	44/114	15/57		14.38%	1.47[0.9,2.4]
Sargent 1995	21/39	11/39		7.91%	1.91[1.07,3.41]
Subtotal (95% CI)	**596**	**377**		**100%**	**1.38[1.16,1.65]**
Total events: 268 (Sumatriptan 50 mg), 123 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=10.93, df=6(P=0.09); I^2=45.11%					
Test for overall effect: Z=3.54(P=0)					
4.8.2 Relief of photophobia at 2 h					
160-104	58/127	19/63		14.66%	1.51[0.99,2.31]
Cutler 1995	20/59	10/61		5.68%	2.07[1.06,4.04]
Diener 2004b	104/148	68/138		40.63%	1.43[1.17,1.74]
Kudrow 2005	42/125	40/134		22.29%	1.13[0.79,1.61]
Sandrini 2002	49/134	17/63		13.35%	1.36[0.85,2.15]
Sargent 1995	11/45	6/47		3.39%	1.91[0.77,4.74]
Subtotal (95% CI)	**638**	**506**		**100%**	**1.42[1.22,1.65]**
Total events: 284 (Sumatriptan 50 mg), 160 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=3.37, df=5(P=0.64); I^2=0%					
Test for overall effect: Z=4.51(P<0.0001)					
4.8.3 Relief of phonophobia at 2 h					
160-104	62/119	21/57		19.05%	1.41[0.97,2.07]
Diener 2004b	86/129	59/128		39.74%	1.45[1.16,1.81]
Kudrow 2005	38/104	30/106		19.94%	1.29[0.87,1.92]
Sandrini 2002	58/138	24/71		21.27%	1.24[0.85,1.82]
Subtotal (95% CI)	**490**	**362**		**100%**	**1.37[1.16,1.6]**
Total events: 244 (Sumatriptan 50 mg), 134 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.6, df=3(P=0.9); I^2=0%					
Test for overall effect: Z=3.82(P=0)					
4.8.4 Relief of photophobia or phonophobia at 2 h					
Ishkanian 2007	49/70	31/65		63.98%	1.47[1.09,1.98]
Pfaffenrath 1998	115/230	12/75		36.02%	3.13[1.83,5.33]
Subtotal (95% CI)	**300**	**140**		**100%**	**2.06[1.55,2.75]**
Total events: 164 (Sumatriptan 50 mg), 43 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=7.37, df=1(P=0.01); I^2=86.44%					
Test for overall effect: Z=4.97(P<0.0001)					



Favours placebo — Favours sumatriptan

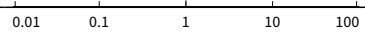
Analysis 4.9. Comparison 4 Oral sumatriptan 50 mg versus placebo, Outcome 9 Relief of associated symptoms in participants with mild baseline pain intensity.

Study or subgroup	Sumatriptan 50 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.9.1 Relief of nausea at 2 h					
Carpay 2004	34/55	0/54		4.57%	67.77[4.26,1078.15]
Winner 2003	44/90	10/81		95.43%	3.96[2.14,7.34]
Subtotal (95% CI)	**145**	**135**		**100%**	**6.88[3.78,12.51]**
Total events: 78 (Sumatriptan 50 mg), 10 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=5.7, df=1(P=0.02); I^2=82.45%					
Test for overall effect: Z=6.32(P<0.0001)					
4.9.2 Relief of photophobia at 2 h					
Carpay 2004	47/81	9/82		20.77%	5.29[2.78,10.06]
Winner 2003	78/156	35/164		79.23%	2.34[1.68,3.27]
Subtotal (95% CI)	**237**	**246**		**100%**	**2.95[2.2,3.97]**
Total events: 125 (Sumatriptan 50 mg), 44 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=5, df=1(P=0.03); I^2=80.01%					
Test for overall effect: Z=7.19(P<0.0001)					
4.9.3 Relief of phonophobia at 2 h					
Carpay 2004	47/78	7/72		20.47%	6.2[3,12.82]
Winner 2003	58/124	30/139		79.53%	2.17[1.5,3.13]
Subtotal (95% CI)	**202**	**211**		**100%**	**2.99[2.15,4.16]**
Total events: 105 (Sumatriptan 50 mg), 37 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=6.8, df=1(P=0.01); I^2=85.3%					
Test for overall effect: Z=6.54(P<0.0001)					



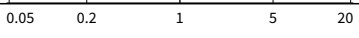
Analysis 4.10. Comparison 4 Oral sumatriptan 50 mg versus placebo, Outcome 10 Relief of functional disability at 2 h.

Study or subgroup	Sumatriptan 50 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
160-104	79/137	34/68		50.06%	1.15[0.87,1.52]
Cutler 1995	24/49	11/53		11.64%	2.36[1.3,4.29]
Sandrini 2002	74/161	21/68		32.53%	1.49[1,2.2]
Sargent 1995	9/31	6/40		5.77%	1.94[0.77,4.86]
Total (95% CI)	**378**	**229**		**100%**	**1.45[1.17,1.79]**
Total events: 186 (Sumatriptan 50 mg), 72 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=5.54, df=3(P=0.14); I^2=45.83%					
Test for overall effect: Z=3.46(P=0)					



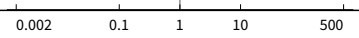
Analysis 4.11. Comparison 4 Oral sumatriptan 50 mg versus placebo, Outcome 11 Any adverse event within 24 h.

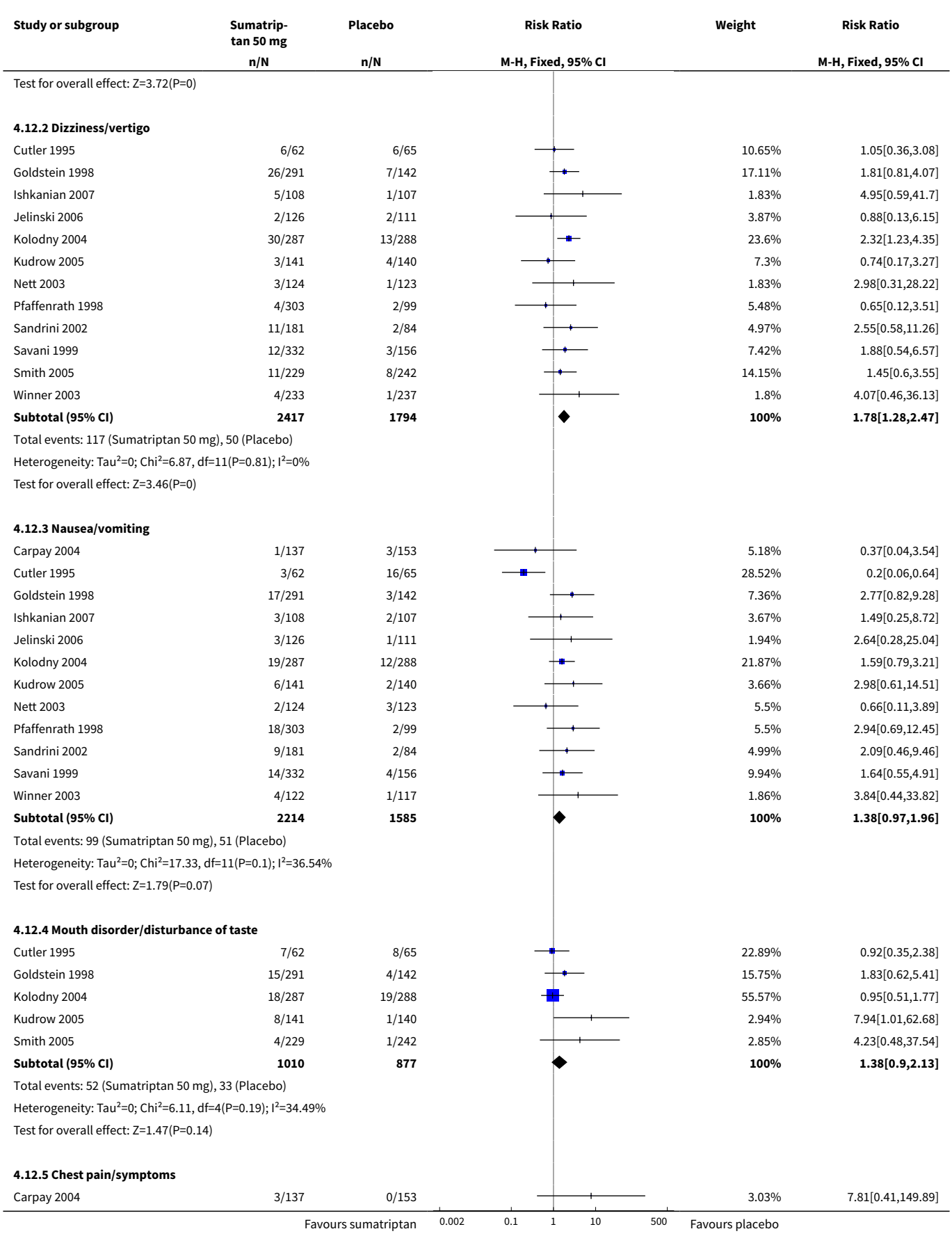
Study or subgroup	Sumatriptan 50 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.11.1 Moderate or severe baseline pain intensity					
Cutler 1995	42/62	48/65		11.02%	0.92[0.73,1.15]
Diener 2004a	19/135	16/153		3.53%	1.35[0.72,2.51]
Diener 2004b	45/226	32/222		7.59%	1.38[0.91,2.09]
Goldstein 1998	134/291	50/142		15.81%	1.31[1.01,1.69]
Ishkanian 2007	21/108	12/108		2.82%	1.75[0.91,3.38]
Kolodny 2004	142/287	102/288		23.95%	1.4[1.15,1.7]
Kudrow 2005	45/141	41/140		9.68%	1.09[0.77,1.55]
Pfaffenrath 1998	82/303	20/99		7.09%	1.34[0.87,2.07]
Savani 1999	82/332	32/156		10.24%	1.2[0.84,1.73]
Smith 2005	55/229	36/241		8.25%	1.61[1.1,2.35]
Subtotal (95% CI)	**2114**	**1614**		**100%**	**1.3[1.17,1.44]**
Total events: 667 (Sumatriptan 50 mg), 389 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=13.04, df=9(P=0.16); I^2=31%					
Test for overall effect: Z=4.95(P<0.0001)					
4.11.2 Mild baseline pain intensity					
Jelinski 2006	25/126	7/111		16.83%	3.15[1.42,6.99]
Nett 2003	10/124	9/123		20.43%	1.1[0.46,2.62]
Pini 1999	10/106	4/82		10.2%	1.93[0.63,5.95]
Tfelt-Hansen 2006	27/53	7/48		16.61%	3.49[1.68,7.28]
Winner 2003	32/233	16/236		35.94%	2.03[1.14,3.59]
Subtotal (95% CI)	**642**	**600**		**100%**	**2.26[1.62,3.16]**
Total events: 104 (Sumatriptan 50 mg), 43 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=4.87, df=4(P=0.3); I^2=17.91%					
Test for overall effect: Z=4.77(P<0.0001)					

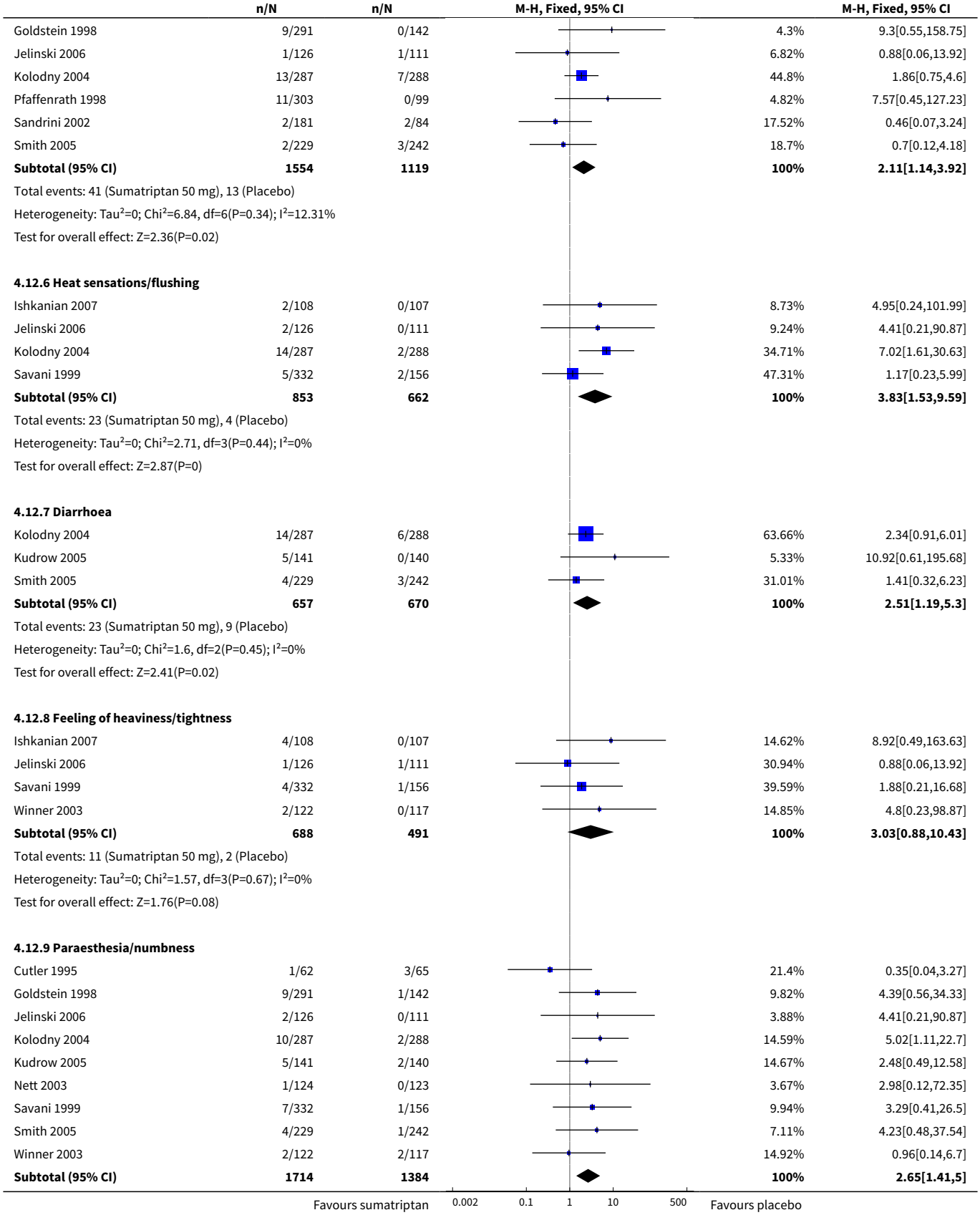


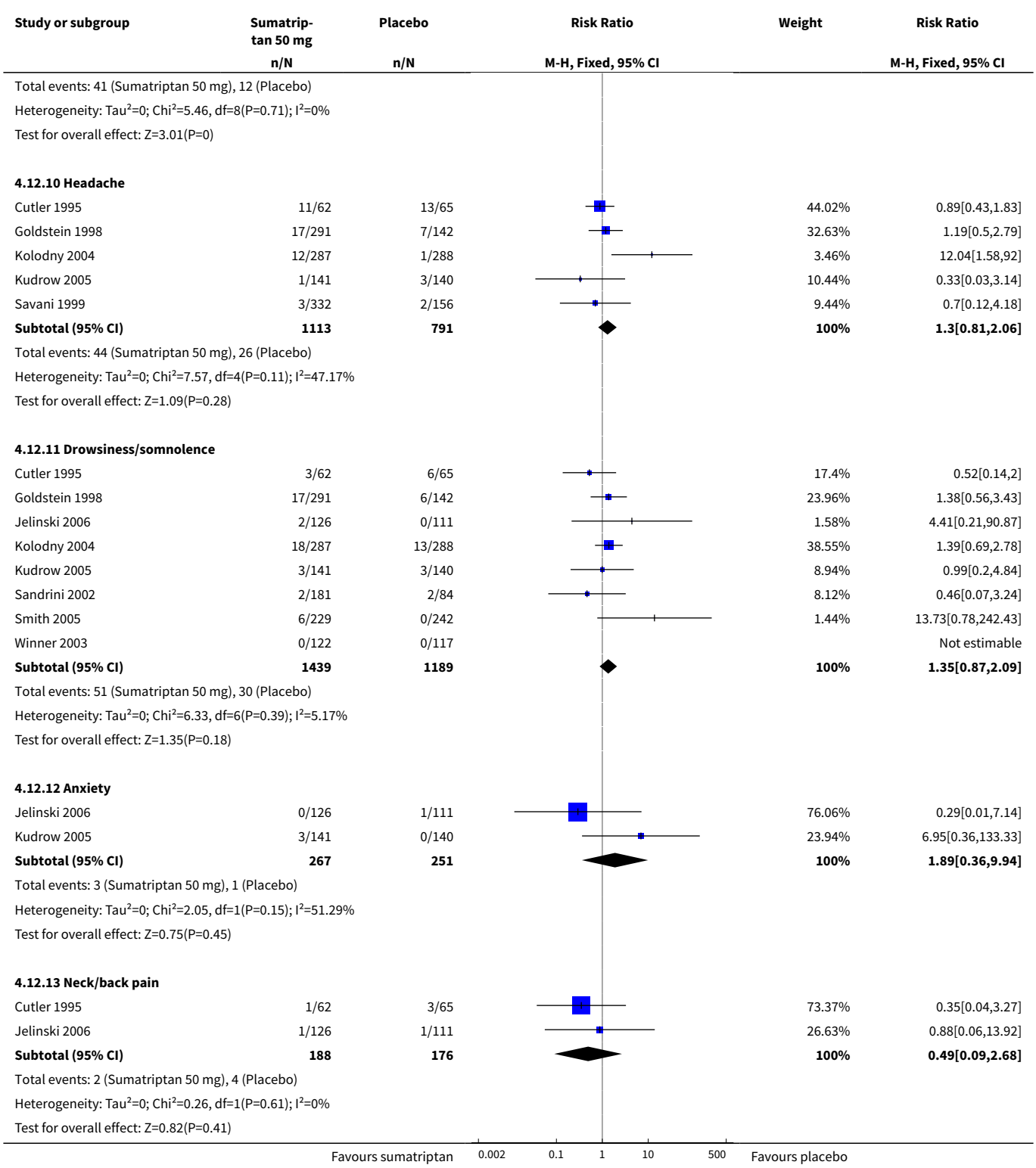
Analysis 4.12. Comparison 4 Oral sumatriptan 50 mg versus placebo, Outcome 12 Individual adverse events.

Study or subgroup	Sumatriptan 50 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.12.1 Malaise/fatigue/asthenia					
Carpay 2004	2/137	1/153		4.51%	2.23[0.2,24.36]
Goldstein 1998	17/291	1/142		6.42%	8.3[1.12,61.71]
Jelinski 2006	6/126	1/111		5.08%	5.29[0.65,43.23]
Kolodny 2004	17/287	6/288		28.59%	2.84[1.14,7.11]
Kudrow 2005	4/141	4/140		19.16%	0.99[0.25,3.89]
Nett 2003	0/124	1/123		7.19%	0.33[0.01,8.04]
Pfaffenrath 1998	8/303	1/99		7.2%	2.61[0.33,20.64]
Sandrini 2002	9/181	2/84		13.04%	2.09[0.46,9.46]
Savani 1999	7/332	1/156		6.5%	3.29[0.41,26.5]
Smith 2005	1/229	0/242		2.32%	3.17[0.13,77.41]
Subtotal (95% CI)	**2151**	**1538**		**100%**	**2.68[1.59,4.5]**
Total events: 71 (Sumatriptan 50 mg), 18 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=5.49, df=9(P=0.79); I^2=0%					



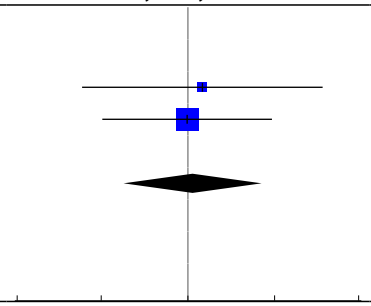






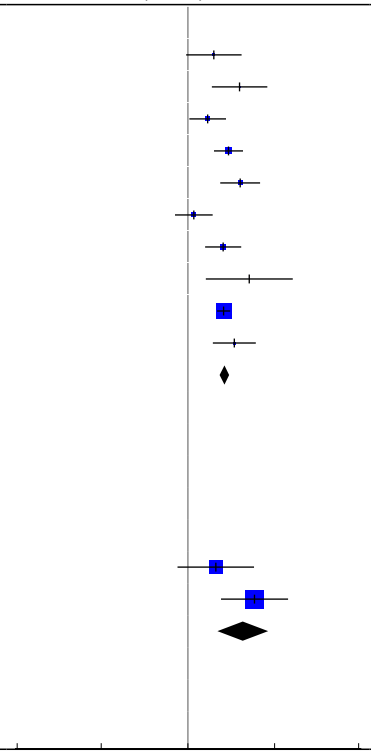
Analysis 4.13. Comparison 4 Oral sumatriptan 50 mg versus placebo, Outcome 13 Any adverse event withdrawal.

Study or subgroup	Sumatriptan 50 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Dahlof 2009	0/136	0/134			Not estimable
Diener 2004b	0/226	0/222			Not estimable
Goldstein 1998	1/291	0/142		30.81%	1.47[0.06,35.84]
Pfaffenrath 1998	3/303	1/99		69.19%	0.98[0.1,9.32]
Total (95% CI)	**956**	**597**		**100%**	**1.13[0.18,7.08]**
Total events: 4 (Sumatriptan 50 mg), 1 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.04, df=1(P=0.84); I^2=0%					
Test for overall effect: Z=0.13(P=0.9)					



Analysis 4.14. Comparison 4 Oral sumatriptan 50 mg versus placebo, Outcome 14 Pain free at 2 h - effect of quality score.

Study or subgroup	Sumatriptan 50 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.14.1 Quality score ≥ 3					
160-104	31/181	8/93		3.61%	1.99[0.95,4.16]
Dahlof 2009	32/136	8/134		2.76%	3.94[1.89,8.24]
Diener 2004a	33/135	22/152		7.08%	1.69[1.04,2.75]
Diener 2004b	83/224	28/222		9.62%	2.94[2,4.32]
Goldstein 1998	209/566	13/141		7.12%	4.01[2.36,6.8]
Ishkanian 2007	26/108	22/107		7.56%	1.17[0.71,1.93]
Lipton 2000	157/870	17/240		9.11%	2.55[1.58,4.12]
Sandrini 2002	33/181	3/84		1.4%	5.1[1.61,16.17]
Sheftell 2005	358/902	137/892		47.11%	2.58[2.17,3.07]
Smith 2005	45/226	14/241		4.63%	3.43[1.94,6.07]
Subtotal (95% CI)	**3529**	**2306**		**100%**	**2.64[2.32,2.99]**
Total events: 1007 (Sumatriptan 50 mg), 272 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=19.84, df=9(P=0.02); I^2=54.64%					
Test for overall effect: Z=14.98(P<0.0001)					
4.14.2 Quality score = 2					
Cutler 1995	10/62	5/65		41.7%	2.1[0.76,5.79]
Savani 1999	63/331	5/154		58.3%	5.86[2.41,14.28]
Subtotal (95% CI)	**393**	**219**		**100%**	**4.29[2.19,8.43]**
Total events: 73 (Sumatriptan 50 mg), 10 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.38, df=1(P=0.12); I^2=58.02%					
Test for overall effect: Z=4.23(P<0.0001)					

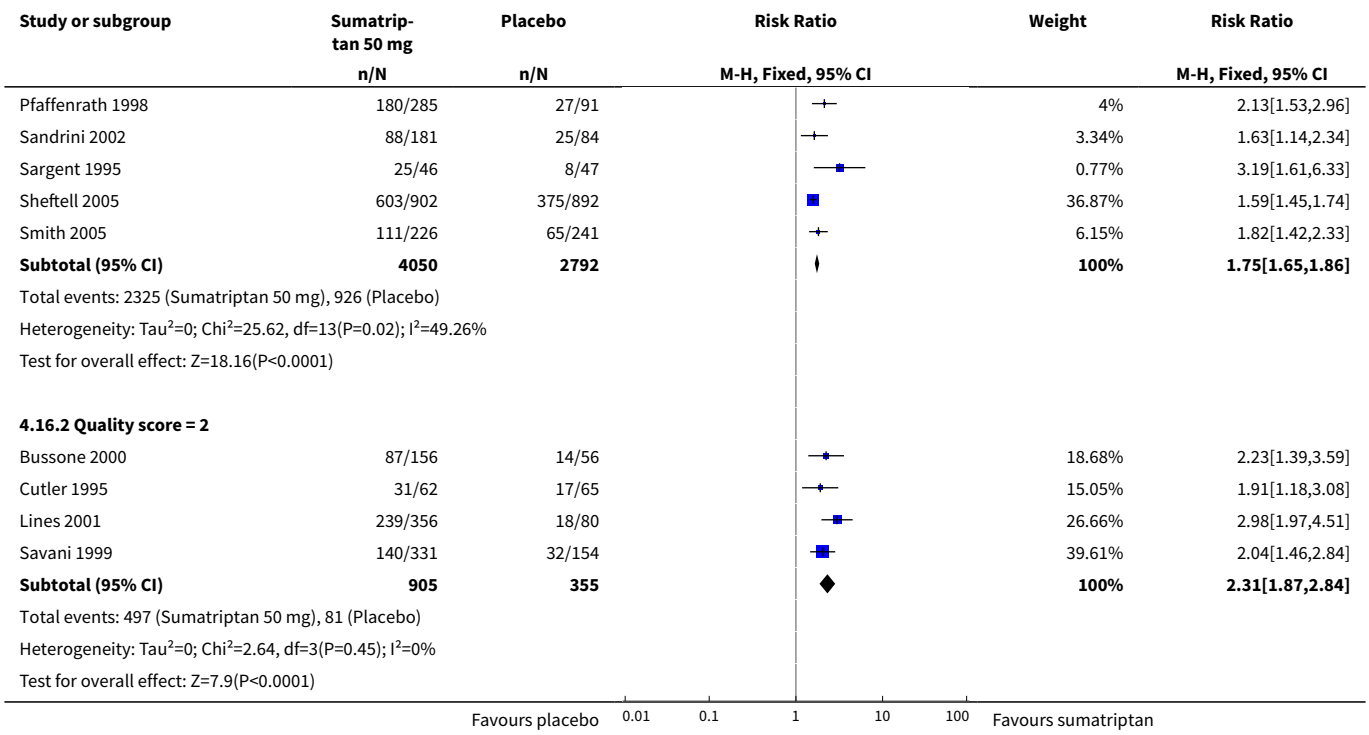


Analysis 4.15. Comparison 4 Oral sumatriptan 50 mg versus placebo, Outcome 15 Headache relief at 1 h - effect of quality score.

Study or subgroup	Sumatriptan 50 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.15.1 All studies					
160-104	48/181	20/93		14.43%	1.23[0.78,1.95]
Diener 2004a	32/135	23/152		11.81%	1.57[0.97,2.54]
Diener 2004b	54/224	25/222		13.71%	2.14[1.38,3.31]
Goldstein 2005	23/46	8/27		5.5%	1.69[0.88,3.23]
Pfaffenrath 1998	123/285	13/91		10.76%	3.02[1.79,5.08]
Sandrini 2002	42/181	10/84		7.46%	1.95[1.03,3.69]
Sargent 1995	6/46	3/47		1.62%	2.04[0.54,7.69]
Savani 1999	74/331	26/154		19.38%	1.32[0.88,1.98]
Smith 2005	52/226	29/241		15.33%	1.91[1.26,2.9]
Subtotal (95% CI)	**1655**	**1111**		**100%**	**1.8[1.52,2.13]**
Total events: 454 (Sumatriptan 50 mg), 157 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=9.79, df=8(P=0.28); I^2=18.29%					
Test for overall effect: Z=6.86(P<0.0001)					
4.15.2 Only quality score ≥ 3					
160-104	48/181	20/93		17.89%	1.23[0.78,1.95]
Diener 2004a	32/135	23/152		14.65%	1.57[0.97,2.54]
Diener 2004b	54/224	25/222		17.01%	2.14[1.38,3.31]
Goldstein 2005	23/46	8/27		6.83%	1.69[0.88,3.23]
Pfaffenrath 1998	123/285	13/91		13.35%	3.02[1.79,5.08]
Sandrini 2002	42/181	10/84		9.25%	1.95[1.03,3.69]
Sargent 1995	6/46	3/47		2.01%	2.04[0.54,7.69]
Smith 2005	52/226	29/241		19.01%	1.91[1.26,2.9]
Subtotal (95% CI)	**1324**	**957**		**100%**	**1.92[1.59,2.31]**
Total events: 380 (Sumatriptan 50 mg), 131 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=7.58, df=7(P=0.37); I^2=7.64%					
Test for overall effect: Z=6.88(P<0.0001)					

Analysis 4.16. Comparison 4 Oral sumatriptan 50 mg versus placebo, Outcome 16 Headache relief at 2 h - effect of quality score.

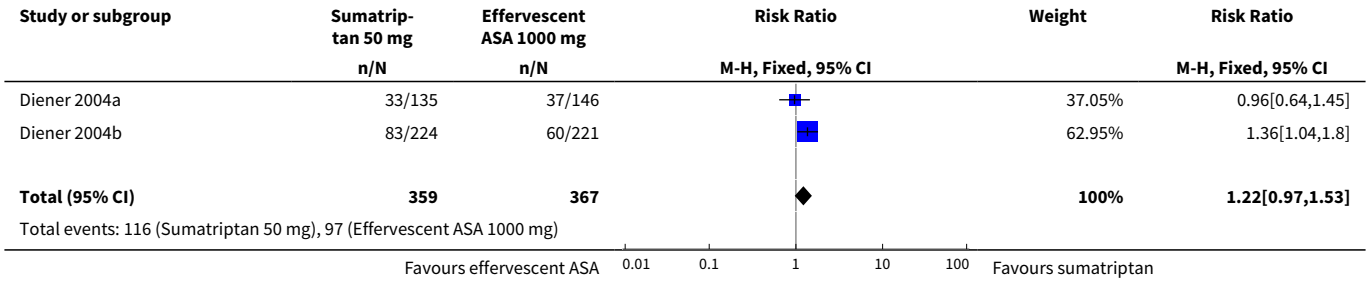
Study or subgroup	Sumatriptan 50 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.16.1 Quality score ≥ 3					
160-104	98/181	34/93		4.39%	1.48[1.1,2]
Dahlof 2009	70/136	36/134		3.55%	1.92[1.39,2.65]
Diener 2004a	66/135	50/152		4.6%	1.49[1.12,1.98]
Diener 2004b	125/224	68/222		6.68%	1.82[1.45,2.29]
Goldstein 1998	385/566	54/141		8.45%	1.78[1.43,2.21]
Goldstein 2005	30/46	14/27		1.72%	1.26[0.83,1.91]
Ishkanian 2007	75/108	46/107		4.52%	1.62[1.26,2.08]
Kudrow 2005	60/144	42/141		4.15%	1.4[1.02,1.92]
Lipton 2000	409/870	82/420		10.81%	2.41[1.96,2.96]



Comparison 5. Oral sumatriptan 50 mg versus effervescent ASA 1000 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain-free at 2 h	2	726	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.97, 1.53]
2 Pain-free at 1 h	2	726	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.53, 1.78]
3 Headache relief at 1 h	2	726	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.61, 0.98]
4 Headache relief at 2 h	2	726	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [1.09, 1.47]
5 Any adverse event within 24 h	2	730	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.85, 1.64]

Analysis 5.1. Comparison 5 Oral sumatriptan 50 mg versus effervescent ASA 1000 mg, Outcome 1 Pain-free at 2 h.



Study or subgroup	Sumatriptan 50 mg n/N	Effervescent ASA 1000 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=1.92, df=1(P=0.17); I²=47.94%					
Test for overall effect: Z=1.69(P=0.09)					

Analysis 5.2. Comparison 5 Oral sumatriptan 50 mg versus effervescent ASA 1000 mg, Outcome 2 Pain-free at 1 h.

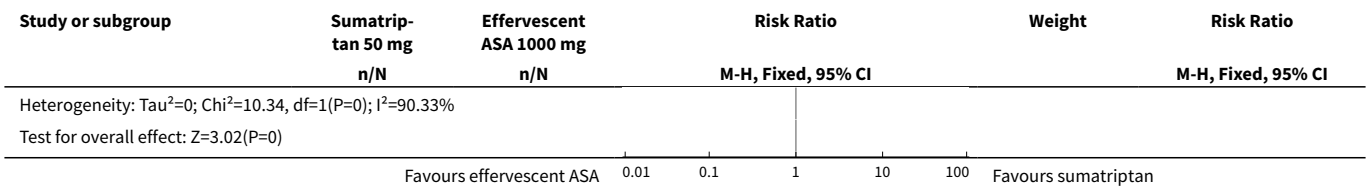
Study or subgroup	Sumatriptan 50 mg n/N	Effervescent ASA 1000 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Diener 2004a	7/135	6/146		29.03%	1.26[0.43,3.66]
Diener 2004b	12/224	14/221		70.97%	0.85[0.4,1.79]
Total (95% CI)	**359**	**367**		**100%**	**0.97[0.53,1.78]**
Total events: 19 (Sumatriptan 50 mg), 20 (Effervescent ASA 1000 mg)					
Heterogeneity: Tau²=0; Chi²=0.36, df=1(P=0.55); I²=0%					
Test for overall effect: Z=0.11(P=0.91)					

Analysis 5.3. Comparison 5 Oral sumatriptan 50 mg versus effervescent ASA 1000 mg, Outcome 3 Headache relief at 1 h.

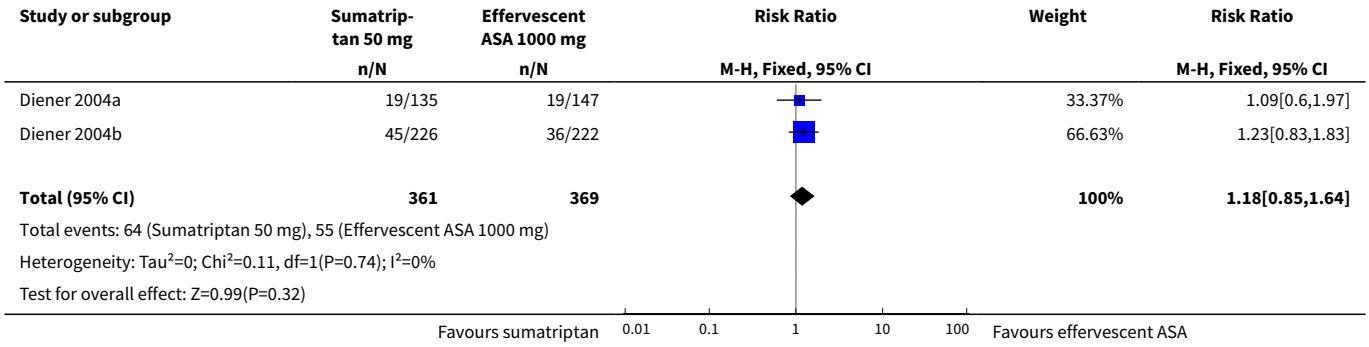
Study or subgroup	Sumatriptan 50 mg n/N	Effervescent ASA 1000 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Diener 2004a	32/135	37/146		31.72%	0.94[0.62,1.41]
Diener 2004b	54/224	76/221		68.28%	0.7[0.52,0.94]
Total (95% CI)	**359**	**367**		**100%**	**0.78[0.61,0.98]**
Total events: 86 (Sumatriptan 50 mg), 113 (Effervescent ASA 1000 mg)					
Heterogeneity: Tau²=0; Chi²=1.25, df=1(P=0.26); I²=19.82%					
Test for overall effect: Z=2.08(P=0.04)					

Analysis 5.4. Comparison 5 Oral sumatriptan 50 mg versus effervescent ASA 1000 mg, Outcome 4 Headache relief at 2 h.

Study or subgroup	Sumatriptan 50 mg n/N	Effervescent ASA 1000 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Diener 2004a	66/135	37/146		23.34%	1.93[1.39,2.68]
Diener 2004b	125/224	116/221		76.66%	1.06[0.9,1.26]
Total (95% CI)	**359**	**367**		**100%**	**1.27[1.09,1.47]**
Total events: 191 (Sumatriptan 50 mg), 153 (Effervescent ASA 1000 mg)					



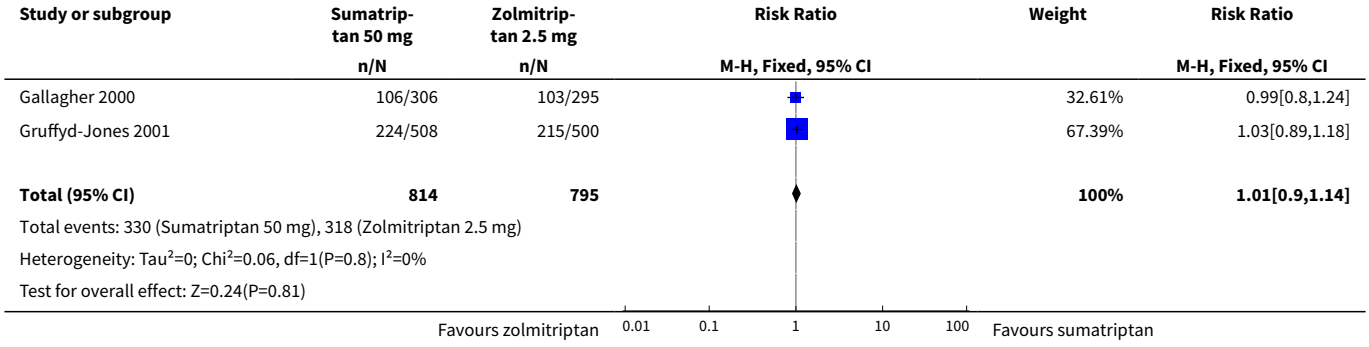
Analysis 5.5. Comparison 5 Oral sumatriptan 50 mg versus effervescent ASA 1000 mg, Outcome 5 Any adverse event within 24 h.



Comparison 6. Oral sumatriptan 50 mg versus zolmitriptan 2.5 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Headache relief at 1 h	2	1609	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.90, 1.14]
2 Headache relief at 2 h	2	1609	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.95, 1.09]
3 Any adverse event within 24 h	2	1771	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.88, 1.15]

Analysis 6.1. Comparison 6 Oral sumatriptan 50 mg versus zolmitriptan 2.5 mg, Outcome 1 Headache relief at 1 h.



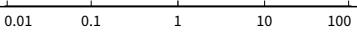
Analysis 6.2. Comparison 6 Oral sumatriptan 50 mg versus zolmitriptan 2.5 mg, Outcome 2 Headache relief at 2 h.

Study or subgroup	Sumatriptan 50 mg n/N	Zolmitriptan 2.5 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Gallagher 2000	182/306	198/295		38.1%	0.89[0.78,1]
Gruffyd-Jones 2001	361/508	325/500		61.9%	1.09[1,1.19]
Total (95% CI)	**814**	**795**		**100%**	**1.01[0.95,1.09]**
Total events: 543 (Sumatriptan 50 mg), 523 (Zolmitriptan 2.5 mg)					
Heterogeneity: Tau^2=0; Chi^2=7.69, df=1(P=0.01); I^2=86.99%					
Test for overall effect: Z=0.4(P=0.69)					

Favours zolmitriptan — Favours sumatriptan

Analysis 6.3. Comparison 6 Oral sumatriptan 50 mg versus zolmitriptan 2.5 mg, Outcome 3 Any adverse event within 24 h.

Study or subgroup	Sumatriptan 50 mg n/N	Zolmitriptan 2.5 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Gallagher 2000	99/338	91/327		32.44%	1.05[0.83,1.34]
Gruffyd-Jones 2001	191/555	192/551		67.56%	0.99[0.84,1.16]
Total (95% CI)	**893**	**878**		**100%**	**1.01[0.88,1.15]**
Total events: 290 (Sumatriptan 50 mg), 283 (Zolmitriptan 2.5 mg)					
Heterogeneity: Tau^2=0; Chi^2=0.19, df=1(P=0.67); I^2=0%					
Test for overall effect: Z=0.13(P=0.9)					



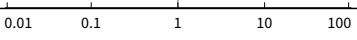
Favours sumatriptan — Favours zolmitriptan

Comparison 7. Oral sumatriptan 50 mg versus zolmitriptan 5 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Headache relief at 1 h	2	1633	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.92, 1.17]
2 Headache relief at 2 h	2	1633	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.95, 1.09]
3 Any adverse event within 24 h	2	1790	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.80, 1.03]

Analysis 7.1. Comparison 7 Oral sumatriptan 50 mg versus zolmitriptan 5 mg, Outcome 1 Headache relief at 1 h.

Study or subgroup	Sumatriptan 50 mg n/N	Zolmitriptan 5 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Gallagher 2000	106/306	114/305		35.8%	0.93[0.75,1.15]
Gruffyd-Jones 2001	224/508	206/514		64.2%	1.1[0.95,1.27]
Total (95% CI)	**814**	**819**		**100%**	**1.04[0.92,1.17]**
Total events: 330 (Sumatriptan 50 mg), 320 (Zolmitriptan 5 mg)					
Heterogeneity: Tau^2=0; Chi^2=1.73, df=1(P=0.19); I^2=42.14%					
Test for overall effect: Z=0.62(P=0.54)					



Favours zolmitriptan — Favours sumatriptan

Analysis 7.2. Comparison 7 Oral sumatriptan 50 mg versus zolmitriptan 5 mg, Outcome 2 Headache relief at 2 h.

Study or subgroup	Sumatriptan 50 mg n/N	Zolmitriptan 5 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Gallagher 2000	182/306	198/305		37.05%	0.92[0.81,1.04]
Gruffyd-Jones 2001	361/508	339/514		62.95%	1.08[0.99,1.17]
Total (95% CI)	**814**	**819**		**100%**	**1.02[0.95,1.09]**
Total events: 543 (Sumatriptan 50 mg), 537 (Zolmitriptan 5 mg)					
Heterogeneity: Tau^2=0; Chi^2=4.57, df=1(P=0.03); I^2=78.09%					
Test for overall effect: Z=0.5(P=0.62)					

Favours zolmitriptan — Favours sumatriptan

Analysis 7.3. Comparison 7 Oral sumatriptan 50 mg versus zolmitriptan 5 mg, Outcome 3 Any adverse event within 24 h.

Study or subgroup	Sumatriptan 50 mg n/N	Zolmitriptan 5 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Gallagher 2000	99/338	111/337		34.61%	0.89[0.71,1.11]
Gruffyd-Jones 2001	191/555	211/560		65.39%	0.91[0.78,1.07]
Total (95% CI)	**893**	**897**		**100%**	**0.91[0.8,1.03]**
Total events: 290 (Sumatriptan 50 mg), 322 (Zolmitriptan 5 mg)					
Heterogeneity: Tau^2=0; Chi^2=0.04, df=1(P=0.85); I^2=0%					
Test for overall effect: Z=1.52(P=0.13)					

Favours sumatriptan — Favours zolmitriptan

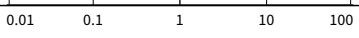
Comparison 8. Oral sumatriptan 50 mg versus rizatriptan 5 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain-free at 2 h	2	2209	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.95, 1.19]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Headache relief at 1 h	2	2209	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.89, 1.11]
3 Headache relief at 2 h	3	2911	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.93, 1.03]
4 Use of rescue medication	2	1696	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.65, 0.93]
4.1 Up to 4 h after initial dosing	2	1696	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.65, 0.93]
5 Any adverse event within 24 h	2	1160	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [1.03, 1.33]

Analysis 8.1. Comparison 8 Oral sumatriptan 50 mg versus rizatriptan 5 mg, Outcome 1 Pain-free at 2 h.

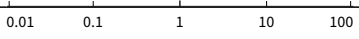
Study or subgroup	Sumatriptan 50 mg n/N	Rizatriptan 5 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Goldstein 1998	209/566	184/557		50.57%	1.12[0.95,1.31]
Kolodny 2004	185/550	179/536		49.43%	1.01[0.85,1.19]
Total (95% CI)	**1116**	**1093**		**100%**	**1.06[0.95,1.19]**
Total events: 394 (Sumatriptan 50 mg), 363 (Rizatriptan 5 mg)					
Heterogeneity: Tau^2=0; Chi^2=0.78, df=1(P=0.38); I^2=0%					
Test for overall effect: Z=1.04(P=0.3)					



Favours rizatriptan — Favours sumatriptan

Analysis 8.2. Comparison 8 Oral sumatriptan 50 mg versus rizatriptan 5 mg, Outcome 2 Headache relief at 1 h.

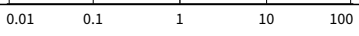
Study or subgroup	Sumatriptan 50 mg n/N	Rizatriptan 5 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Goldstein 1998	218/566	209/557		51.61%	1.03[0.88,1.19]
Kolodny 2004	191/550	195/536		48.39%	0.95[0.81,1.12]
Total (95% CI)	**1116**	**1093**		**100%**	**0.99[0.89,1.11]**
Total events: 409 (Sumatriptan 50 mg), 404 (Rizatriptan 5 mg)					
Heterogeneity: Tau^2=0; Chi^2=0.42, df=1(P=0.52); I^2=0%					
Test for overall effect: Z=0.15(P=0.88)					



Favours rizatriptan — Favours sumatriptan

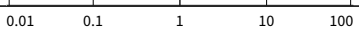
Analysis 8.3. Comparison 8 Oral sumatriptan 50 mg versus rizatriptan 5 mg, Outcome 3 Headache relief at 2 h.

Study or subgroup	Sumatriptan 50 mg n/N	Rizatriptan 5 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Goldstein 1998	349/563	379/557		39.7%	0.91[0.84,0.99]
Kolodny 2004	361/550	352/536		37.15%	1[0.92,1.09]
Lines 2001	239/356	220/349		23.15%	1.07[0.96,1.19]
Total (95% CI)	**1469**	**1442**		**100%**	**0.98[0.93,1.03]**
Total events: 949 (Sumatriptan 50 mg), 951 (Rizatriptan 5 mg)					
Heterogeneity: Tau^2=0; Chi^2=5.22, df=2(P=0.07); I^2=61.7%					
Test for overall effect: Z=0.76(P=0.44)					



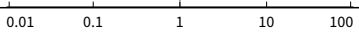
Analysis 8.4. Comparison 8 Oral sumatriptan 50 mg versus rizatriptan 5 mg, Outcome 4 Use of rescue medication.

Study or subgroup	Sumatriptan 50 mg n/N	Rizatriptan 5 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
8.4.1 Up to 4 h after initial dosing					
Goldstein 1998	108/566	128/557		60.41%	0.83[0.66,1.04]
Kolodny 2004	59/285	85/288		39.59%	0.7[0.53,0.94]
Subtotal (95% CI)	**851**	**845**		**100%**	**0.78[0.65,0.93]**
Total events: 167 (Sumatriptan 50 mg), 213 (Rizatriptan 5 mg)					
Heterogeneity: Tau^2=0; Chi^2=0.81, df=1(P=0.37); I^2=0%					
Test for overall effect: Z=2.73(P=0.01)					
Total (95% CI)	**851**	**845**		**100%**	**0.78[0.65,0.93]**
Total events: 167 (Sumatriptan 50 mg), 213 (Rizatriptan 5 mg)					
Heterogeneity: Tau^2=0; Chi^2=0.81, df=1(P=0.37); I^2=0%					
Test for overall effect: Z=2.73(P=0.01)					



Analysis 8.5. Comparison 8 Oral sumatriptan 50 mg versus rizatriptan 5 mg, Outcome 5 Any adverse event within 24 h.

Study or subgroup	Sumatriptan 50 mg n/N	Rizatriptan 5 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Goldstein 1998	134/291	129/294		54.12%	1.05[0.88,1.26]
Kolodny 2004	142/287	109/288		45.88%	1.31[1.08,1.58]
Total (95% CI)	**578**	**582**		**100%**	**1.17[1.03,1.33]**
Total events: 276 (Sumatriptan 50 mg), 238 (Rizatriptan 5 mg)					
Heterogeneity: Tau^2=0; Chi^2=2.74, df=1(P=0.1); I^2=63.47%					
Test for overall effect: Z=2.34(P=0.02)					

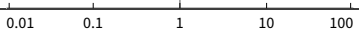


Comparison 9. Oral sumatriptan 50 mg versus rizatriptan 10 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain-free at 2 h	2	2230	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.80, 1.00]
2 Headache relief at 1 h	2	2230	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.81, 0.99]
3 Headache relief at 2 h	2	2227	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.86, 0.97]
4 Use of rescue medication	2	1714	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.80, 1.17]
4.1 Up to 4 h after initial dosing	2	1714	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.80, 1.17]
5 Any adverse event within 24 h	2	1177	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.92, 1.17]

Analysis 9.1. Comparison 9 Oral sumatriptan 50 mg versus rizatriptan 10 mg, Outcome 1 Pain-free at 2 h.

Study or subgroup	Sumatriptan 50 mg n/N	Rizatriptan 10 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Goldstein 1998	209/566	232/567		52.64%	0.9[0.78,1.04]
Kolodny 2004	185/550	208/547		47.36%	0.88[0.75,1.04]
Total (95% CI)	**1116**	**1114**		**100%**	**0.89[0.8,1]**
Total events: 394 (Sumatriptan 50 mg), 440 (Rizatriptan 10 mg)					
Heterogeneity: Tau^2=0; Chi^2=0.03, df=1(P=0.86); I^2=0%					
Test for overall effect: Z=2.04(P=0.04)					



Favours rizatriptan — Favours sumatriptan

Analysis 9.2. Comparison 9 Oral sumatriptan 50 mg versus rizatriptan 10 mg, Outcome 2 Headache relief at 1 h.

Study or subgroup	Sumatriptan 50 mg n/N	Rizatriptan 10 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Goldstein 1998	218/566	236/567		51.66%	0.93[0.8,1.07]
Kolodny 2004	191/550	220/547		48.34%	0.86[0.74,1.01]
Total (95% CI)	**1116**	**1114**		**100%**	**0.9[0.81,0.99]**
Total events: 409 (Sumatriptan 50 mg), 456 (Rizatriptan 10 mg)					
Heterogeneity: Tau^2=0; Chi^2=0.42, df=1(P=0.52); I^2=0%					
Test for overall effect: Z=2.07(P=0.04)					

Favours rizatriptan — Favours sumatriptan

Analysis 9.3. Comparison 9 Oral sumatriptan 50 mg versus rizatriptan 10 mg, Outcome 3 Headache relief at 2 h.

Study or subgroup	Sumatriptan 50 mg n/N	Rizatriptan 10 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Goldstein 1998	349/563	408/567		52.15%	0.86[0.79,0.94]
Kolodny 2004	361/550	372/547		47.85%	0.97[0.89,1.05]
Total (95% CI)	**1113**	**1114**		**100%**	**0.91[0.86,0.97]**
Total events: 710 (Sumatriptan 50 mg), 780 (Rizatriptan 10 mg)					
Heterogeneity: Tau^2=0; Chi^2=3.6, df=1(P=0.06); I^2=72.21%					
Test for overall effect: Z=3.11(P=0)					

Analysis 9.4. Comparison 9 Oral sumatriptan 50 mg versus rizatriptan 10 mg, Outcome 4 Use of rescue medication.

Study or subgroup	Sumatriptan 50 mg n/N	Rizatriptan 10 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
9.4.1 Up to 4 h after initial dosing					
Goldstein 1998	108/566	108/567		62.14%	1[0.79,1.27]
Kolodny 2004	59/285	67/296		37.86%	0.91[0.67,1.25]
Subtotal (95% CI)	**851**	**863**		**100%**	**0.97[0.8,1.17]**
Total events: 167 (Sumatriptan 50 mg), 175 (Rizatriptan 10 mg)					
Heterogeneity: Tau^2=0; Chi^2=0.21, df=1(P=0.65); I^2=0%					
Test for overall effect: Z=0.33(P=0.74)					
Total (95% CI)	**851**	**863**		**100%**	**0.97[0.8,1.17]**
Total events: 167 (Sumatriptan 50 mg), 175 (Rizatriptan 10 mg)					
Heterogeneity: Tau^2=0; Chi^2=0.21, df=1(P=0.65); I^2=0%					
Test for overall effect: Z=0.33(P=0.74)					

Analysis 9.5. Comparison 9 Oral sumatriptan 50 mg versus rizatriptan 10 mg, Outcome 5 Any adverse event within 24 h.

Study or subgroup	Sumatriptan 50 mg n/N	Rizatriptan 10 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Goldstein 1998	134/291	137/305		49.35%	1.03[0.86,1.22]
Kolodny 2004	142/287	139/294		50.65%	1.05[0.88,1.24]
Total (95% CI)	**578**	**599**		**100%**	**1.04[0.92,1.17]**
Total events: 276 (Sumatriptan 50 mg), 276 (Rizatriptan 10 mg)					
Heterogeneity: Tau^2=0; Chi^2=0.03, df=1(P=0.87); I^2=0%					
Test for overall effect: Z=0.57(P=0.57)					

Comparison 10. Oral sumatriptan 50 mg versus eletriptan 40 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain-free at 2 h	2	721	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.55, 0.98]
2 Headache relief at 1 h	2	721	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.77, 1.28]
3 Headache relief at 2 h	2	721	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.75, 0.97]
4 Relief of associated symptoms	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Relief of nausea at 2 h	2	374	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.60, 0.95]
4.2 Relief of photophobia at 2 h	2	528	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.69, 1.00]
4.3 Relief of phonophobia at 2 h	2	517	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.73, 1.04]
5 Relief of functional disability at 2 h	2	590	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.72, 0.96]

Analysis 10.1. Comparison 10 Oral sumatriptan 50 mg versus eletriptan 40 mg, Outcome 1 Pain-free at 2 h.

Study or subgroup	Sumatriptan 50 mg n/N	Eletriptan 40 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
160-104	31/181	34/184		38.94%	0.93[0.6,1.44]
Sandrini 2002	33/181	52/175		61.06%	0.61[0.42,0.9]
Total (95% CI)	**362**	**359**		**100%**	**0.74[0.55,0.98]**
Total events: 64 (Sumatriptan 50 mg), 86 (Eletriptan 40 mg)					
Heterogeneity: Tau^2=0; Chi^2=1.91, df=1(P=0.17); I^2=47.71%					
Test for overall effect: Z=2.09(P=0.04)					

Analysis 10.2. Comparison 10 Oral sumatriptan 50 mg versus eletriptan 40 mg, Outcome 2 Headache relief at 1 h.

Study or subgroup	Sumatriptan 50 mg n/N	Eletriptan 40 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
160-104	48/181	38/184		41.61%	1.28[0.88,1.86]
Sandrini 2002	42/181	52/175		58.39%	0.78[0.55,1.11]
Total (95% CI)	**362**	**359**		**100%**	**0.99[0.77,1.28]**
Total events: 90 (Sumatriptan 50 mg), 90 (Eletriptan 40 mg)					
Heterogeneity: Tau^2=0; Chi^2=3.64, df=1(P=0.06); I^2=72.52%					
Test for overall effect: Z=0.08(P=0.94)					

Analysis 10.3. Comparison 10 Oral sumatriptan 50 mg versus eletriptan 40 mg, Outcome 3 Headache relief at 2 h.

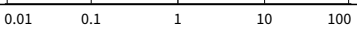
Study or subgroup	Sumatriptan 50 mg n/N	Eletriptan 40 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
160-104	98/181	109/184		49.61%	0.91[0.76,1.09]
Sandrini 2002	88/181	108/175		50.39%	0.79[0.65,0.95]
Total (95% CI)	**362**	**359**		**100%**	**0.85[0.75,0.97]**
Total events: 186 (Sumatriptan 50 mg), 217 (Eletriptan 40 mg)					
Heterogeneity: Tau^2=0; Chi^2=1.24, df=1(P=0.27); I^2=19.39%					
Test for overall effect: Z=2.43(P=0.01)					

Analysis 10.4. Comparison 10 Oral sumatriptan 50 mg versus eletriptan 40 mg, Outcome 4 Relief of associated symptoms.

Study or subgroup	Sumatriptan 50 mg n/N	Eletriptan 40 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
10.4.1 Relief of nausea at 2 h					
160-104	27/74	28/73		30.16%	0.95[0.63,1.45]
Sandrini 2002	44/114	65/113		69.84%	0.67[0.51,0.89]
Subtotal (95% CI)	**188**	**186**		**100%**	**0.76[0.6,0.95]**
Total events: 71 (Sumatriptan 50 mg), 93 (Eletriptan 40 mg)					
Heterogeneity: Tau^2=0; Chi^2=1.85, df=1(P=0.17); I^2=46.02%					
Test for overall effect: Z=2.36(P=0.02)					
10.4.2 Relief of photophobia at 2 h					
160-104	58/127	61/129		46.39%	0.97[0.74,1.26]
Sandrini 2002	49/134	71/138		53.61%	0.71[0.54,0.94]
Subtotal (95% CI)	**261**	**267**		**100%**	**0.83[0.69,1]**
Total events: 107 (Sumatriptan 50 mg), 132 (Eletriptan 40 mg)					
Heterogeneity: Tau^2=0; Chi^2=2.49, df=1(P=0.11); I^2=59.88%					
Test for overall effect: Z=1.93(P=0.05)					
10.4.3 Relief of phonophobia at 2 h					
160-104	62/119	59/116		43.28%	1.02[0.8,1.31]
Sandrini 2002	58/138	80/144		56.72%	0.76[0.59,0.97]
Subtotal (95% CI)	**257**	**260**		**100%**	**0.87[0.73,1.04]**
Total events: 120 (Sumatriptan 50 mg), 139 (Eletriptan 40 mg)					
Heterogeneity: Tau^2=0; Chi^2=2.91, df=1(P=0.09); I^2=65.66%					
Test for overall effect: Z=1.54(P=0.12)					

Analysis 10.5. Comparison 10 Oral sumatriptan 50 mg versus eletriptan 40 mg, Outcome 5 Relief of functional disability at 2 h.

Study or subgroup	Sumatriptan 50 mg n/N	Eletriptan 40 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
160-104	79/137	84/140		45.69%	0.96[0.79,1.17]
Sandrini 2002	74/161	96/152		54.31%	0.73[0.59,0.89]
Total (95% CI)	**298**	**292**		**100%**	**0.83[0.72,0.96]**
Total events: 153 (Sumatriptan 50 mg), 180 (Eletriptan 40 mg)					
Heterogeneity: Tau^2=0; Chi^2=3.65, df=1(P=0.06); I^2=72.62%					
Test for overall effect: Z=2.49(P=0.01)					

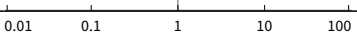


Comparison 11. Oral sumatriptan 50 mg versus eletriptan 80 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain-free at 2 h	2	706	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.44, 0.76]
2 Headache relief at 1 h	2	706	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.57, 0.91]
3 Headache relief at 2 h	2	706	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.69, 0.89]
4 Relief of associated symptoms	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Relief of nausea at 2 h	2	370	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.66, 1.08]
4.2 Relief of photophobia at 2 h	2	508	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.60, 0.86]
5 Relief of functional disability at 2 h	2	570	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.73, 0.97]

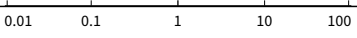
Analysis 11.1. Comparison 11 Oral sumatriptan 50 mg versus eletriptan 80 mg, Outcome 1 Pain-free at 2 h.

Study or subgroup	Sumatriptan 50 mg n/N	Eletriptan 80 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
160-104	31/181	45/180		42.16%	0.69[0.46,1.03]
Sandrini 2002	33/181	59/164		57.84%	0.51[0.35,0.73]
Total (95% CI)	**362**	**344**		**100%**	**0.58[0.44,0.76]**
Total events: 64 (Sumatriptan 50 mg), 104 (Eletriptan 80 mg)					
Heterogeneity: Tau^2=0; Chi^2=1.15, df=1(P=0.28); I^2=13.05%					
Test for overall effect: Z=3.88(P=0)					



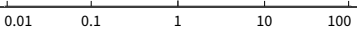
Analysis 11.2. Comparison 11 Oral sumatriptan 50 mg versus eletriptan 80 mg, Outcome 2 Headache relief at 1 h.

Study or subgroup	Sumatriptan 50 mg n/N	Eletriptan 80 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
160-104	48/181	61/180		50.13%	0.78[0.57,1.07]
Sandrini 2002	42/181	58/164		49.87%	0.66[0.47,0.92]
Total (95% CI)	**362**	**344**		**100%**	**0.72[0.57,0.91]**
Total events: 90 (Sumatriptan 50 mg), 119 (Eletriptan 80 mg)					
Heterogeneity: Tau^2=0; Chi^2=0.56, df=1(P=0.45); I^2=0%					
Test for overall effect: Z=2.8(P=0.01)					



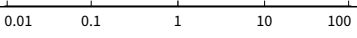
Analysis 11.3. Comparison 11 Oral sumatriptan 50 mg versus eletriptan 80 mg, Outcome 3 Headache relief at 2 h.

Study or subgroup	Sumatriptan 50 mg n/N	Eletriptan 80 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
160-104	98/181	119/180		51.52%	0.82[0.69,0.97]
Sandrini 2002	88/181	107/164		48.48%	0.75[0.62,0.9]
Total (95% CI)	**362**	**344**		**100%**	**0.78[0.69,0.89]**
Total events: 186 (Sumatriptan 50 mg), 226 (Eletriptan 80 mg)					
Heterogeneity: Tau^2=0; Chi^2=0.54, df=1(P=0.46); I^2=0%					
Test for overall effect: Z=3.81(P=0)					

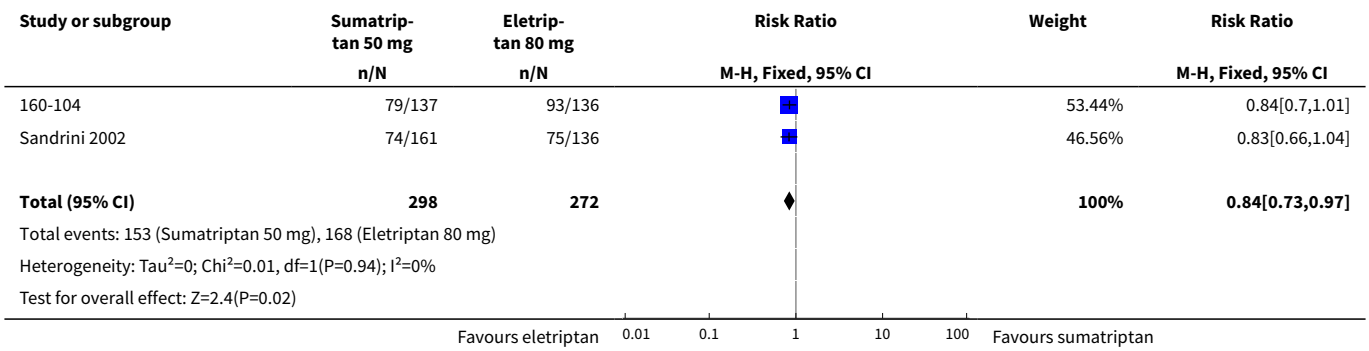


Analysis 11.4. Comparison 11 Oral sumatriptan 50 mg versus eletriptan 80 mg, Outcome 4 Relief of associated symptoms.

Study or subgroup	Sumatriptan 50 mg n/N	Eletriptan 80 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
11.4.1 Relief of nausea at 2 h					
160-104	27/74	27/73		32.99%	0.99[0.65,1.51]
Sandrini 2002	44/114	54/109		67.01%	0.78[0.58,1.05]
Subtotal (95% CI)	**188**	**182**		**100%**	**0.85[0.66,1.08]**
Total events: 71 (Sumatriptan 50 mg), 81 (Eletriptan 80 mg)					
Heterogeneity: Tau^2=0; Chi^2=0.8, df=1(P=0.37); I^2=0%					
Test for overall effect: Z=1.33(P=0.18)					
11.4.2 Relief of photophobia at 2 h					
160-104	58/127	75/131		50.69%	0.8[0.63,1.01]
Sandrini 2002	49/134	67/116		49.31%	0.63[0.48,0.83]
Subtotal (95% CI)	**261**	**247**		**100%**	**0.72[0.6,0.86]**
Total events: 107 (Sumatriptan 50 mg), 142 (Eletriptan 80 mg)					
Heterogeneity: Tau^2=0; Chi^2=1.56, df=1(P=0.21); I^2=35.9%					
Test for overall effect: Z=3.63(P=0)					



Analysis 11.5. Comparison 11 Oral sumatriptan 50 mg versus eletriptan 80 mg, Outcome 5 Relief of functional disability at 2 h.



Comparison 12. Oral sumatriptan 100 mg versus placebo

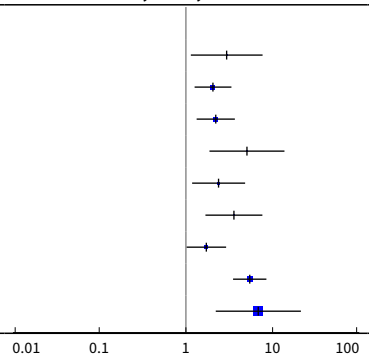
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain-free at 2 h	19		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Moderate or severe baseline pain intensity	15	6571	Risk Ratio (M-H, Fixed, 95% CI)	3.20 [2.84, 3.62]
1.2 Mild baseline pain intensity	4	1240	Risk Ratio (M-H, Fixed, 95% CI)	2.41 [2.06, 2.81]
2 Pain-free at 1 h	10		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Moderate or severe baseline pain intensity	6	3176	Risk Ratio (M-H, Fixed, 95% CI)	3.97 [2.33, 6.77]
2.2 Mild baseline pain intensity	4	1240	Risk Ratio (M-H, Fixed, 95% CI)	2.21 [1.76, 2.78]
3 Headache relief at 1 h	10	3983	Risk Ratio (M-H, Fixed, 95% CI)	1.88 [1.62, 2.18]
4 Headache relief at 2 h	20	7811	Risk Ratio (M-H, Fixed, 95% CI)	1.93 [1.82, 2.04]
5 24 h sustained pain free	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Moderate or severe baseline pain intensity	5	2891	Risk Ratio (M-H, Fixed, 95% CI)	2.81 [2.30, 3.44]
5.2 Mild baseline pain intensity	3	771	Risk Ratio (M-H, Fixed, 95% CI)	3.24 [2.33, 4.51]
6 24 h sustained headache relief	5	4116	Risk Ratio (M-H, Fixed, 95% CI)	2.12 [1.87, 2.39]
7 Use of rescue medication	9		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Up to 24 h after initial dosing	6	2810	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.52, 0.62]
7.2 Up to 4 h after initial dosing	3	1027	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.47, 0.65]

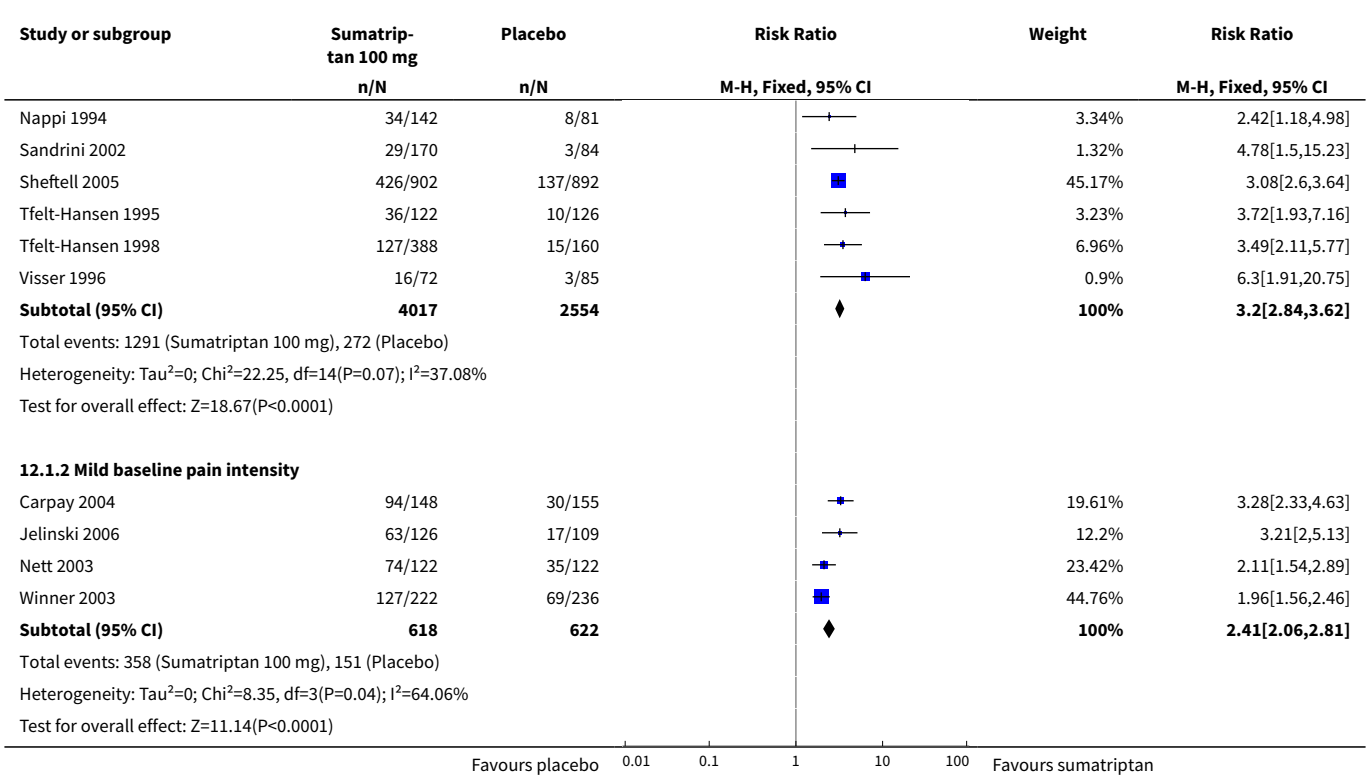
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Relief of associated symptoms in participants with moderate or severe baseline pain intensity	16		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Relief of nausea at 2 h	14	2996	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [1.37, 1.69]
8.2 Relief of photophobia at 2 h	9	2494	Risk Ratio (M-H, Fixed, 95% CI)	1.85 [1.63, 2.11]
8.3 Relief of phonophobia at 2 h	7	2118	Risk Ratio (M-H, Fixed, 95% CI)	1.83 [1.59, 2.11]
8.4 Relief of photophobia or phonophobia at 2 h	5	1073	Risk Ratio (M-H, Fixed, 95% CI)	2.02 [1.66, 2.46]
9 Relief of associated symptoms in participants with mild baseline pain intensity	2	1140	Risk Ratio (M-H, Fixed, 95% CI)	3.73 [3.04, 4.57]
9.1 Relief of nausea at 2 h	2	265	Risk Ratio (M-H, Fixed, 95% CI)	5.89 [3.18, 10.91]
9.2 Relief of photophobia at 2 h	2	475	Risk Ratio (M-H, Fixed, 95% CI)	3.23 [2.41, 4.33]
9.3 Relief of phonophobia at 2 h	2	400	Risk Ratio (M-H, Fixed, 95% CI)	3.70 [2.69, 5.08]
10 Relief of functional disability at 2 h	6	1827	Risk Ratio (M-H, Fixed, 95% CI)	1.87 [1.65, 2.11]
11 Any adverse event within 24 h	15		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 Moderate or severe baseline pain intensity	12	3257	Risk Ratio (M-H, Fixed, 95% CI)	1.69 [1.50, 1.91]
11.2 Mild baseline pain intensity	3	941	Risk Ratio (M-H, Fixed, 95% CI)	2.75 [1.87, 4.05]
12 Individual adverse events	20		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 Malaise/fatigue/asthenia	16	4844	Risk Ratio (M-H, Fixed, 95% CI)	2.36 [1.64, 3.38]
12.2 Dizziness/vertigo	16	4959	Risk Ratio (M-H, Fixed, 95% CI)	2.34 [1.60, 3.42]
12.3 Nausea/vomiting	19	5284	Risk Ratio (M-H, Fixed, 95% CI)	1.71 [1.32, 2.22]
12.4 Mouth disorder/disturbance of taste	5	1047	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.78, 2.39]
12.5 Chest pain/symptoms	12	3452	Risk Ratio (M-H, Fixed, 95% CI)	3.04 [1.71, 5.40]
12.6 Heat sensations/flushing	2	786	Risk Ratio (M-H, Fixed, 95% CI)	3.55 [0.68, 18.61]
12.7 Palpitations/tachycardia	2	499	Risk Ratio (M-H, Fixed, 95% CI)	3.53 [0.75, 16.66]
12.8 Feeling of heaviness/tightness	5	1317	Risk Ratio (M-H, Fixed, 95% CI)	4.14 [1.34, 12.77]
12.9 Paraesthesia/numbness	12	3154	Risk Ratio (M-H, Fixed, 95% CI)	3.97 [2.16, 7.29]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.10 Headache	3	411	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.41, 1.45]
12.11 Drowsiness/somnolence	13	3710	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [1.01, 2.29]
12.12 Abdominal pain/discomfort/dyspepsia	5	1357	Risk Ratio (M-H, Fixed, 95% CI)	2.80 [1.35, 5.80]
12.13 Anxiety	2	499	Risk Ratio (M-H, Fixed, 95% CI)	1.90 [0.36, 9.92]
12.14 Neck/back pain	6	1508	Risk Ratio (M-H, Fixed, 95% CI)	1.87 [0.76, 4.58]
13 Any adverse event withdrawal	9	2744	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [0.77, 3.47]
14 Headache relief at 2 h - effect of formulation	20		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 Standard tablet	18	5774	Risk Ratio (M-H, Fixed, 95% CI)	2.00 [1.86, 2.16]
14.2 Dispersible/rapid-release tablet	2	2037	Risk Ratio (M-H, Fixed, 95% CI)	1.80 [1.65, 1.96]
15 Pain-free at 2 h - effect of quality score	15		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1 Quality score ≥ 3	12	5939	Risk Ratio (M-H, Fixed, 95% CI)	3.26 [2.87, 3.71]
15.2 Quality score = 2	3	632	Risk Ratio (M-H, Fixed, 95% CI)	2.68 [1.80, 4.00]
16 Headache relief at 2 h - effect of quality score	20		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 Quality score ≥ 3	16	6771	Risk Ratio (M-H, Fixed, 95% CI)	1.85 [1.74, 1.97]
16.2 Quality score = 2	4	1040	Risk Ratio (M-H, Fixed, 95% CI)	2.57 [2.14, 3.09]

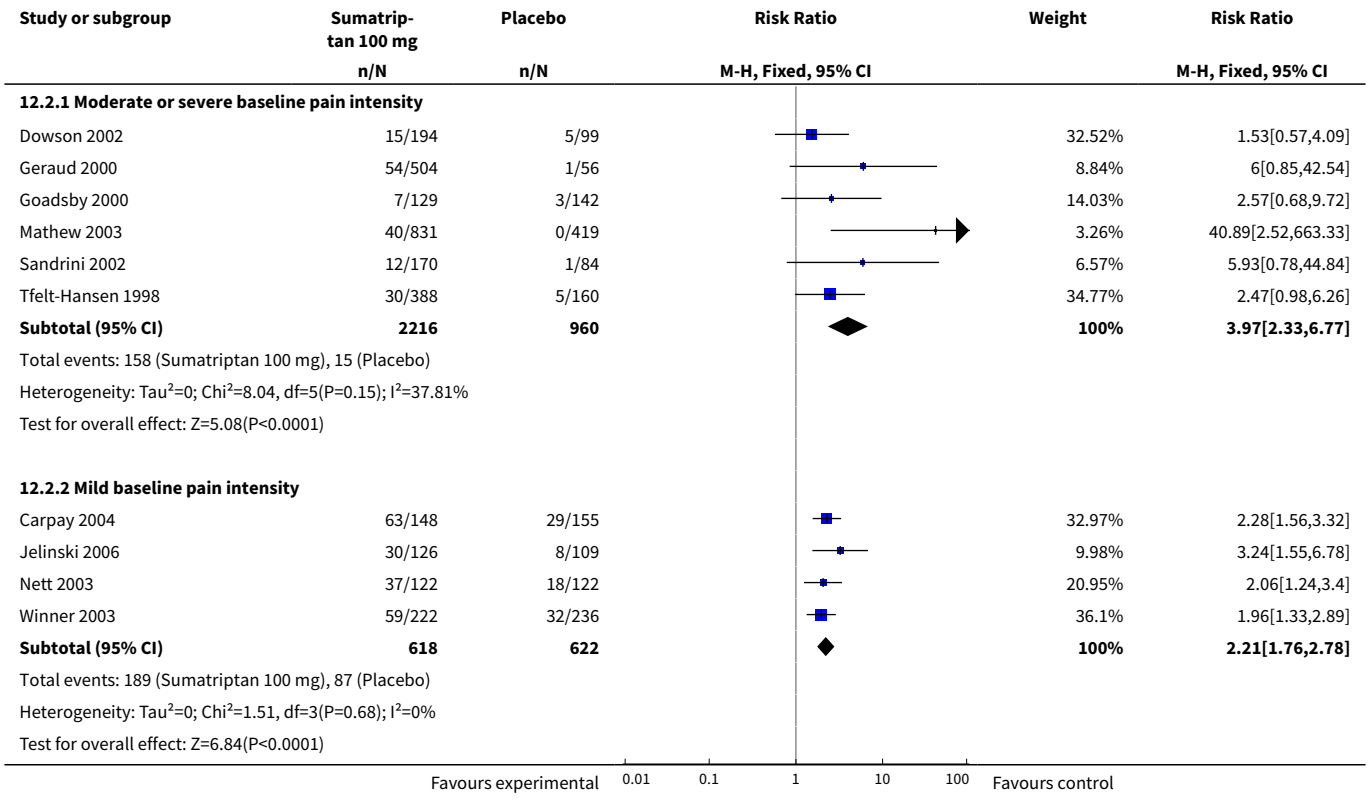
Analysis 12.1. Comparison 12 Oral sumatriptan 100 mg versus placebo, Outcome 1 Pain-free at 2 h.

Study or subgroup	Sumatriptan 100 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
12.1.1 Moderate or severe baseline pain intensity					
Cutler 1995	15/66	5/65		1.65%	2.95[1.14,7.66]
Dodick 2002	64/193	16/99		6.93%	2.05[1.26,3.35]
Dowson 2002	65/194	15/99		6.51%	2.21[1.33,3.67]
Ensink 1991	34/131	4/78		1.64%	5.06[1.87,13.72]
Geraud 2000	150/504	7/56		4.13%	2.38[1.18,4.82]
Goadsby 2000	26/129	8/142		2.5%	3.58[1.68,7.62]
Kaniecki 2006	32/131	18/127		5.99%	1.72[1.02,2.91]
Mathew 2003	216/831	20/419		8.72%	5.45[3.5,8.48]
Myllyla 1998	21/42	3/41		1%	6.83[2.21,21.17]



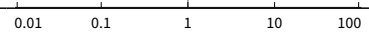


Analysis 12.2. Comparison 12 Oral sumatriptan 100 mg versus placebo, Outcome 2 Pain-free at 1 h.



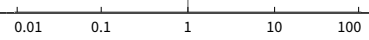
Analysis 12.3. Comparison 12 Oral sumatriptan 100 mg versus placebo, Outcome 3 Headache relief at 1 h.

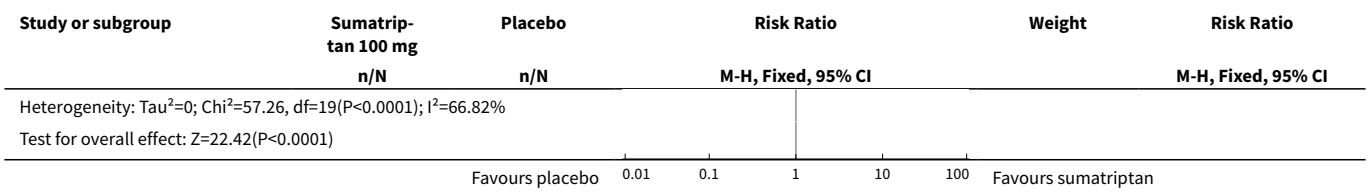
Study or subgroup	Sumatriptan 100 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Dowson 2002	73/194	29/99		15.88%	1.28[0.9,1.83]
Geraud 2000	171/504	11/56		8.19%	1.73[1,2.97]
Goadsby 2000	23/129	15/142		5.9%	1.69[0.92,3.09]
Havanka 2000	34/98	18/91		7.72%	1.75[1.07,2.88]
Mathew 2003	214/831	44/419		24.18%	2.45[1.81,3.32]
Pfaffenrath 1998	100/277	13/91		8.09%	2.53[1.49,4.28]
Sandrini 2002	45/170	10/84		5.53%	2.22[1.18,4.19]
Sargent 1995	10/46	3/47		1.23%	3.41[1,11.59]
Tfelt-Hansen 1998	108/388	32/160		18.73%	1.39[0.98,1.97]
Visser 1996	17/72	12/85		4.55%	1.67[0.86,3.27]
Total (95% CI)	**2709**	**1274**		**100%**	**1.88[1.62,2.18]**
Total events: 795 (Sumatriptan 100 mg), 187 (Placebo)					
Heterogeneity: $Tau^2=0$; $Chi^2=13.01$, df=9(P=0.16); $I^2=30.84\%$					
Test for overall effect: Z=8.38(P<0.0001)					



Analysis 12.4. Comparison 12 Oral sumatriptan 100 mg versus placebo, Outcome 4 Headache relief at 2 h.

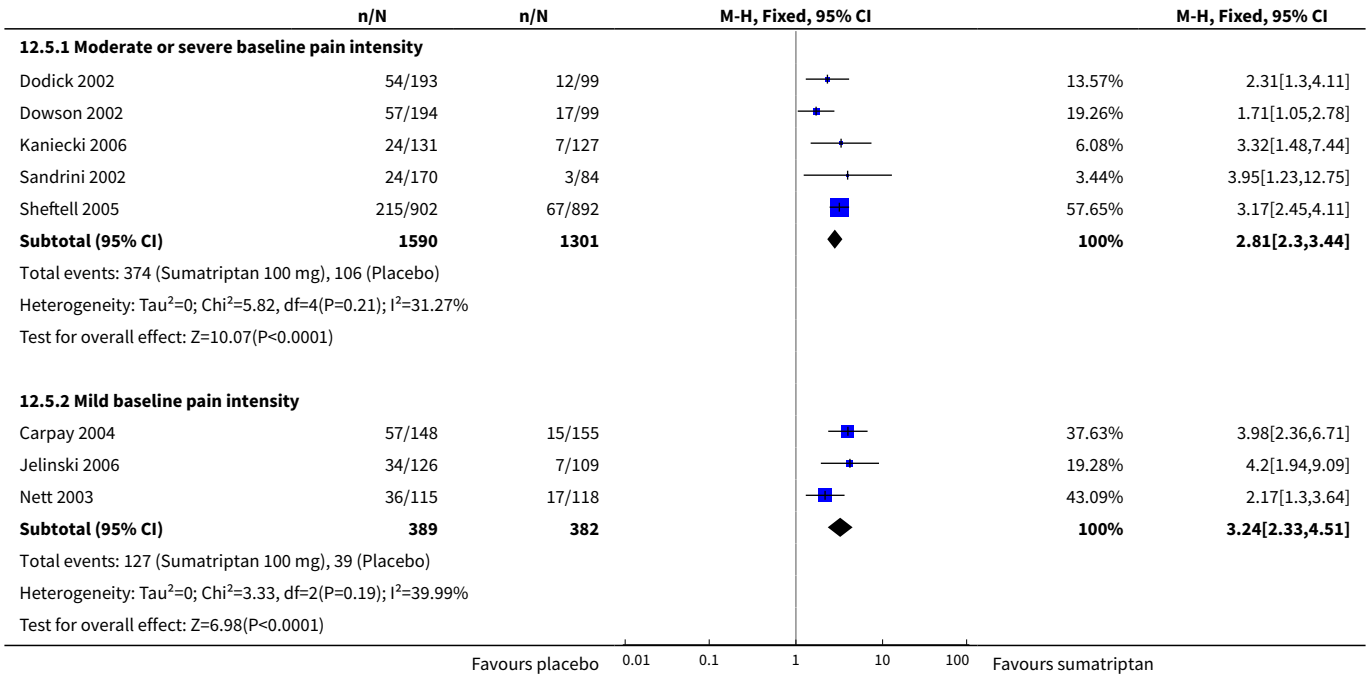
Study or subgroup	Sumatriptan 100 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Cutler 1995	37/66	17/65		1.55%	2.14[1.35,3.4]
Dahlof 1991	180/275	48/182		5.22%	2.48[1.92,3.21]
Dowson 2002	123/194	42/99		5.02%	1.49[1.16,1.93]
Ensink 1991	60/131	14/78		1.58%	2.55[1.53,4.25]
Geraud 2000	304/504	24/56		3.9%	1.41[1.03,1.92]
Goadsby 1991	45/89	9/93		0.79%	5.22[2.72,10.05]
Goadsby 2000	63/129	30/142		2.58%	2.31[1.61,3.33]
Havanka 2000	59/98	28/91		2.62%	1.96[1.38,2.77]
Kaniecki 2006	64/131	47/127		4.31%	1.32[0.99,1.76]
Mathew 2003	471/831	105/419		12.6%	2.26[1.9,2.7]
Myllyla 1998	33/42	12/41		1.1%	2.68[1.63,4.43]
Nappi 1994	73/142	25/81		2.87%	1.67[1.16,2.39]
Patten 1991	95/142	22/101		2.32%	3.07[2.09,4.52]
Pfaffenrath 1998	175/277	27/91		3.67%	2.13[1.53,2.96]
Sandrini 2002	85/170	25/84		3.02%	1.68[1.17,2.41]
Sargent 1995	26/46	8/47		0.71%	3.32[1.68,6.56]
Sheftell 2005	649/902	375/892		34.04%	1.71[1.57,1.87]
Tfelt-Hansen 1995	63/122	30/126		2.66%	2.17[1.52,3.1]
Tfelt-Hansen 1998	239/388	64/160		8.18%	1.54[1.25,1.89]
Visser 1996	33/72	15/85		1.24%	2.6[1.54,4.38]
Total (95% CI)	**4751**	**3060**		**100%**	**1.93[1.82,2.04]**
Total events: 2877 (Sumatriptan 100 mg), 967 (Placebo)					





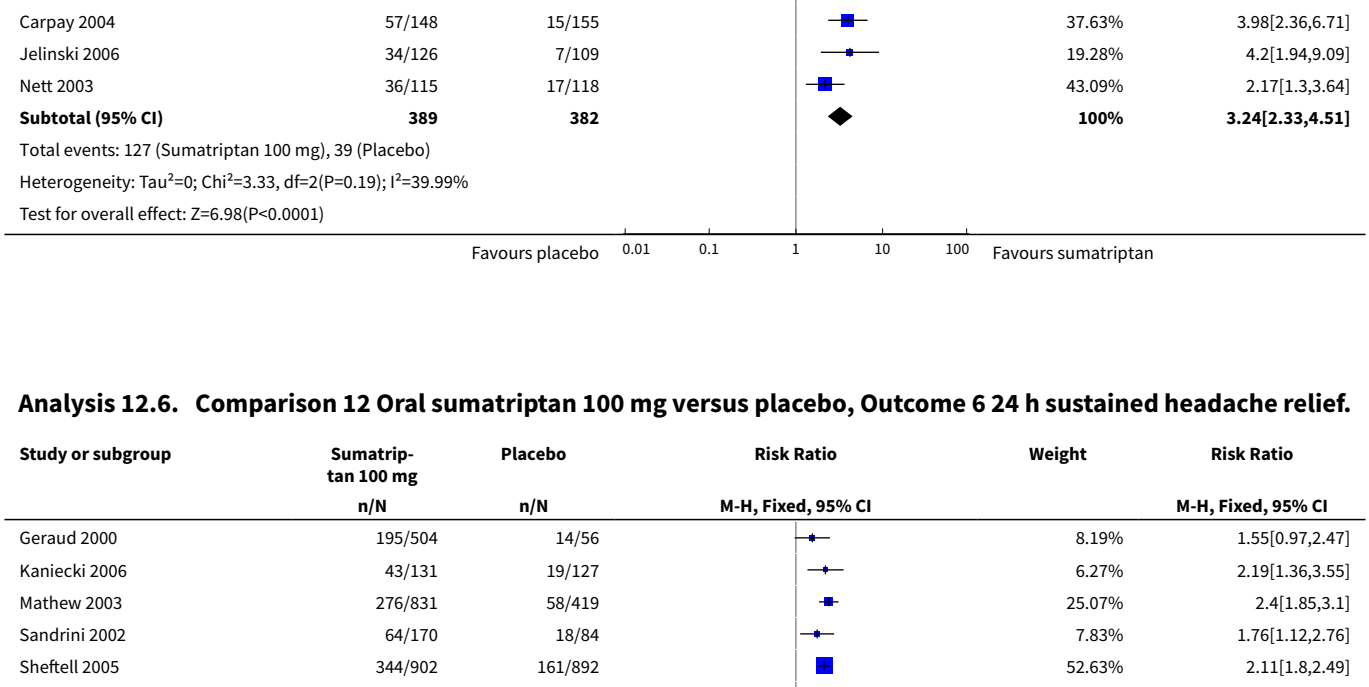
Analysis 12.5. Comparison 12 Oral sumatriptan 100 mg versus placebo, Outcome 5 24 h sustained pain free.

Study or subgroup	Sumatriptan 100 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
12.5.1 Moderate or severe baseline pain intensity					
Dodick 2002	54/193	12/99		13.57%	2.31[1.3,4.11]
Dowson 2002	57/194	17/99		19.26%	1.71[1.05,2.78]
Kaniecki 2006	24/131	7/127		6.08%	3.32[1.48,7.44]
Sandrini 2002	24/170	3/84		3.44%	3.95[1.23,12.75]
Sheftell 2005	215/902	67/892		57.65%	3.17[2.45,4.11]
Subtotal (95% CI)	**1590**	**1301**		**100%**	**2.81[2.3,3.44]**
Total events: 374 (Sumatriptan 100 mg), 106 (Placebo)					
Heterogeneity: Tau²=0; Chi²=5.82, df=4(P=0.21); I²=31.27%					
Test for overall effect: Z=10.07(P<0.0001)					
12.5.2 Mild baseline pain intensity					
Carpay 2004	57/148	15/155		37.63%	3.98[2.36,6.71]
Jelinski 2006	34/126	7/109		19.28%	4.2[1.94,9.09]
Nett 2003	36/115	17/118		43.09%	2.17[1.3,3.64]
Subtotal (95% CI)	**389**	**382**		**100%**	**3.24[2.33,4.51]**
Total events: 127 (Sumatriptan 100 mg), 39 (Placebo)					
Heterogeneity: Tau²=0; Chi²=3.33, df=2(P=0.19); I²=39.99%					
Test for overall effect: Z=6.98(P<0.0001)					



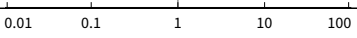
Analysis 12.6. Comparison 12 Oral sumatriptan 100 mg versus placebo, Outcome 6 24 h sustained headache relief.

Study or subgroup	Sumatriptan 100 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Geraud 2000	195/504	14/56		8.19%	1.55[0.97,2.47]
Kaniecki 2006	43/131	19/127		6.27%	2.19[1.36,3.55]
Mathew 2003	276/831	58/419		25.07%	2.4[1.85,3.1]
Sandrini 2002	64/170	18/84		7.83%	1.76[1.12,2.76]
Sheftell 2005	344/902	161/892		52.63%	2.11[1.8,2.49]
Total (95% CI)	**2538**	**1578**		**100%**	**2.12[1.87,2.39]**
Total events: 922 (Sumatriptan 100 mg), 270 (Placebo)					
Heterogeneity: Tau²=0; Chi²=3.31, df=4(P=0.51); I²=0%					
Test for overall effect: Z=11.95(P<0.0001)					



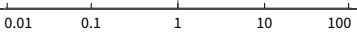
Analysis 12.7. Comparison 12 Oral sumatriptan 100 mg versus placebo, Outcome 7 Use of rescue medication.

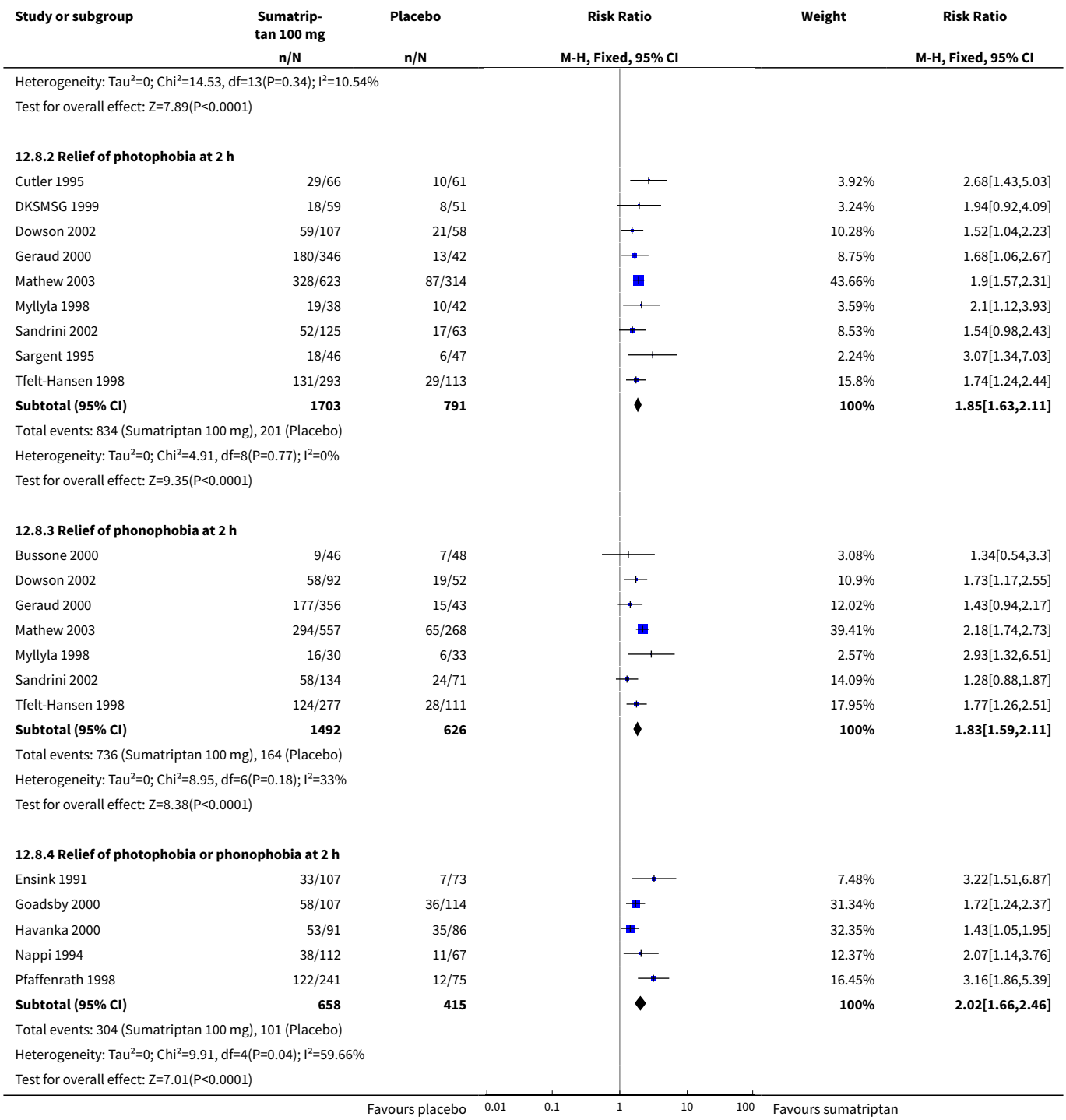
Study or subgroup	Sumatriptan 100 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
12.7.1 Up to 24 h after initial dosing					
Dodick 2002	66/193	52/99		10.49%	0.65[0.5,0.85]
Geraud 2000	192/504	32/56		8.79%	0.67[0.52,0.86]
Goadsby 2000	37/129	75/142		10.89%	0.54[0.4,0.74]
Havanka 2000	25/98	60/91		9.49%	0.39[0.27,0.56]
Mathew 2003	224/831	222/419		45.03%	0.51[0.44,0.59]
Tfelt-Hansen 1995	77/122	102/126		15.31%	0.78[0.66,0.91]
Subtotal (95% CI)	**1877**	**933**		**100%**	**0.57[0.52,0.62]**
Total events: 621 (Sumatriptan 100 mg), 543 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=23.74, df=5(P=0); I^2=78.94%					
Test for overall effect: Z=12.28(P<0.0001)					
12.7.2 Up to 4 h after initial dosing					
Dowson 2002	63/194	55/99		31.93%	0.58[0.45,0.76]
Goadsby 1991	39/94	83/94		36.38%	0.47[0.37,0.6]
Tfelt-Hansen 1998	77/387	51/159		31.69%	0.62[0.46,0.84]
Subtotal (95% CI)	**675**	**352**		**100%**	**0.55[0.47,0.65]**
Total events: 179 (Sumatriptan 100 mg), 189 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.35, df=2(P=0.31); I^2=14.74%					
Test for overall effect: Z=7.3(P<0.0001)					



Analysis 12.8. Comparison 12 Oral sumatriptan 100 mg versus placebo, Outcome 8 Relief of associated symptoms in participants with moderate or severe baseline pain intensity.

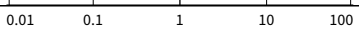
Study or subgroup	Sumatriptan 100 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
12.8.1 Relief of nausea at 2 h					
Cutler 1995	27/50	26/54		6.5%	1.12[0.77,1.63]
DKSMSG 1999	13/58	5/47		1.44%	2.11[0.81,5.49]
Dowson 2002	66/126	24/67		8.14%	1.46[1.02,2.1]
Geraud 2000	97/273	3/25		1.43%	2.96[1.01,8.66]
Goadsby 2000	44/82	39/90		9.67%	1.24[0.91,1.69]
Havanka 2000	47/76	33/72		8.81%	1.35[0.99,1.83]
Mathew 2003	252/515	94/268		32.14%	1.4[1.16,1.68]
Myllyla 1998	1/20	0/20		0.13%	3[0.13,69.52]
Nappi 1994	27/101	9/59		2.95%	1.75[0.89,3.47]
Pfaffenrath 1998	93/176	19/64		7.24%	1.78[1.19,2.66]
Sandrini 2002	56/122	15/57		5.31%	1.74[1.08,2.81]
Sargent 1995	27/40	11/39		2.9%	2.39[1.39,4.13]
Tfelt-Hansen 1995	26/84	9/81		2.38%	2.79[1.39,5.58]
Tfelt-Hansen 1998	104/232	30/98		10.96%	1.46[1.05,2.04]
Subtotal (95% CI)	**1955**	**1041**		**100%**	**1.52[1.37,1.69]**
Total events: 880 (Sumatriptan 100 mg), 317 (Placebo)					





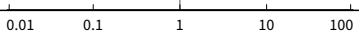
Analysis 12.9. Comparison 12 Oral sumatriptan 100 mg versus placebo, Outcome 9 Relief of associated symptoms in participants with mild baseline pain intensity.

Study or subgroup	Sumatriptan 100 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
12.9.1 Relief of nausea at 2 h					
Carpay 2004	24/55	0/54		0.59%	48.13[3,771.95]
Winner 2003	34/75	10/81		11.17%	3.67[1.95,6.9]
Subtotal (95% CI)	**130**	**135**		**11.75%**	**5.89[3.18,10.91]**
Total events: 58 (Sumatriptan 100 mg), 10 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=4.35, df=1(P=0.04); I^2=77.02%					
Test for overall effect: Z=5.63(P<0.0001)					
12.9.2 Relief of photophobia at 2 h					
Carpay 2004	52/85	9/82		10.64%	5.57[2.94,10.56]
Winner 2003	79/144	35/164		38.01%	2.57[1.85,3.57]
Subtotal (95% CI)	**229**	**246**		**48.65%**	**3.23[2.41,4.33]**
Total events: 131 (Sumatriptan 100 mg), 44 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=4.64, df=1(P=0.03); I^2=78.46%					
Test for overall effect: Z=7.81(P<0.0001)					
12.9.3 Relief of phonophobia at 2 h					
Carpay 2004	48/76	7/72		8.35%	6.5[3.15,13.41]
Winner 2003	72/113	30/139		31.25%	2.95[2.09,4.17]
Subtotal (95% CI)	**189**	**211**		**39.6%**	**3.7[2.69,5.08]**
Total events: 120 (Sumatriptan 100 mg), 37 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=3.95, df=1(P=0.05); I^2=74.7%					
Test for overall effect: Z=8.09(P<0.0001)					
Total (95% CI)	**548**	**592**		**100%**	**3.73[3.04,4.57]**
Total events: 309 (Sumatriptan 100 mg), 91 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=13.69, df=5(P=0.02); I^2=63.47%					
Test for overall effect: Z=12.63(P<0.0001)					
Test for subgroup differences: Chi^2=2.99, df=1 (P=0.22), I^2=33.04%					

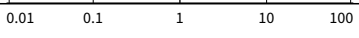


Analysis 12.10. Comparison 12 Oral sumatriptan 100 mg versus placebo, Outcome 10 Relief of functional disability at 2 h.

Study or subgroup	Sumatriptan 100 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Cutler 1995	28/55	11/53		4.27%	2.45[1.36,4.41]
Goadsby 2000	62/110	44/130		15.36%	1.67[1.24,2.23]
Havanka 2000	55/92	24/79		9.84%	1.97[1.35,2.86]
Mathew 2003	424/681	114/344		57.69%	1.88[1.6,2.21]
Sandrini 2002	67/145	21/68		10.89%	1.5[1.01,2.22]
Sargent 1995	15/30	6/40		1.96%	3.33[1.47,7.57]
Total (95% CI)	**1113**	**714**		**100%**	**1.87[1.65,2.11]**
Total events: 651 (Sumatriptan 100 mg), 220 (Placebo)					



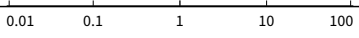
Study or subgroup	Sumatriptan 100 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=4.62, df=5(P=0.46); I²=0%					
Test for overall effect: Z=10.09(P<0.0001)					



Favours placebo — Favours sumatriptan

Analysis 12.11. Comparison 12 Oral sumatriptan 100 mg versus placebo, Outcome 11 Any adverse event within 24 h.

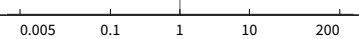
Study or subgroup	Sumatriptan 100 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
12.11.1 Moderate or severe baseline pain intensity					
Cutler 1995	42/66	48/65		15.71%	0.86[0.68,1.09]
DKSMSG 1999	43/130	26/131		8.41%	1.67[1.09,2.54]
Dowson 2002	43/194	6/99		2.58%	3.66[1.61,8.3]
Ensink 1991	57/149	19/84		7.89%	1.69[1.08,2.64]
Geraud 2000	279/492	13/56		7.58%	2.44[1.51,3.96]
Goadsby 2000	52/129	24/142		7.42%	2.39[1.57,3.63]
Havanka 2000	25/98	21/91		7.07%	1.11[0.67,1.83]
Nappi 1994	24/69	4/19		2.04%	1.65[0.65,4.18]
Pfaffenrath 1998	111/298	20/99		9.75%	1.84[1.21,2.8]
Tfelt-Hansen 1995	38/125	18/126		5.82%	2.13[1.29,3.52]
Tfelt-Hansen 1998	202/388	51/160		23.45%	1.63[1.28,2.09]
Visser 1996	15/33	5/14		2.28%	1.27[0.57,2.82]
Subtotal (95% CI)	**2171**	**1086**		**100%**	**1.69[1.5,1.91]**
Total events: 931 (Sumatriptan 100 mg), 255 (Placebo)					
Heterogeneity: Tau²=0; Chi²=44.76, df=11(P<0.0001); I²=75.42%					
Test for overall effect: Z=8.44(P<0.0001)					
12.11.2 Mild baseline pain intensity					
Jelinski 2006	34/127	7/111		23.39%	4.25[1.96,9.19]
Nett 2003	20/122	9/123		28.06%	2.24[1.06,4.72]
Winner 2003	35/222	16/236		48.56%	2.33[1.33,4.08]
Subtotal (95% CI)	**471**	**470**		**100%**	**2.75[1.87,4.05]**
Total events: 89 (Sumatriptan 100 mg), 32 (Placebo)					
Heterogeneity: Tau²=0; Chi²=1.85, df=2(P=0.4); I²=0%					
Test for overall effect: Z=5.14(P<0.0001)					



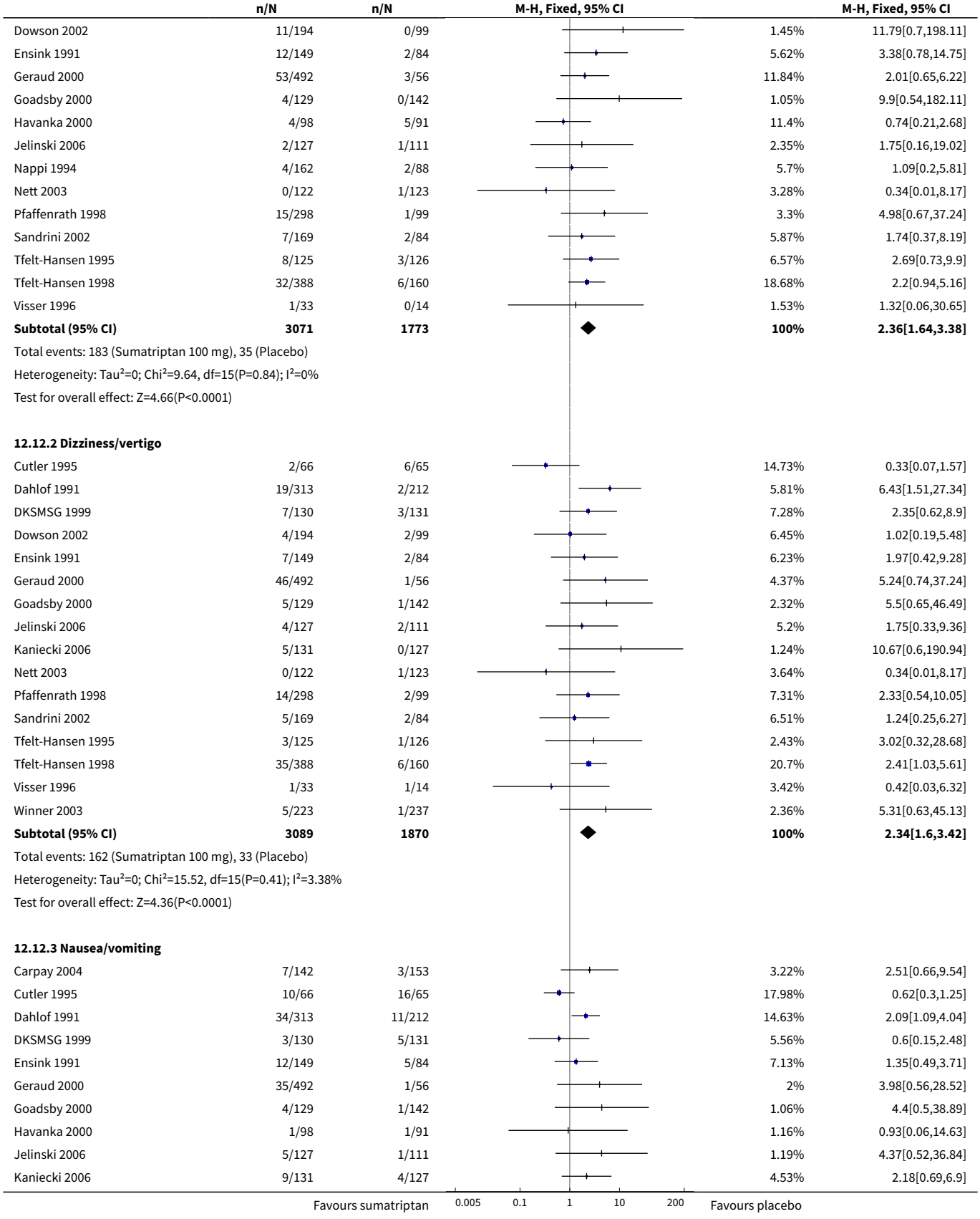
Favours sumatriptan — Favours placebo

Analysis 12.12. Comparison 12 Oral sumatriptan 100 mg versus placebo, Outcome 12 Individual adverse events.

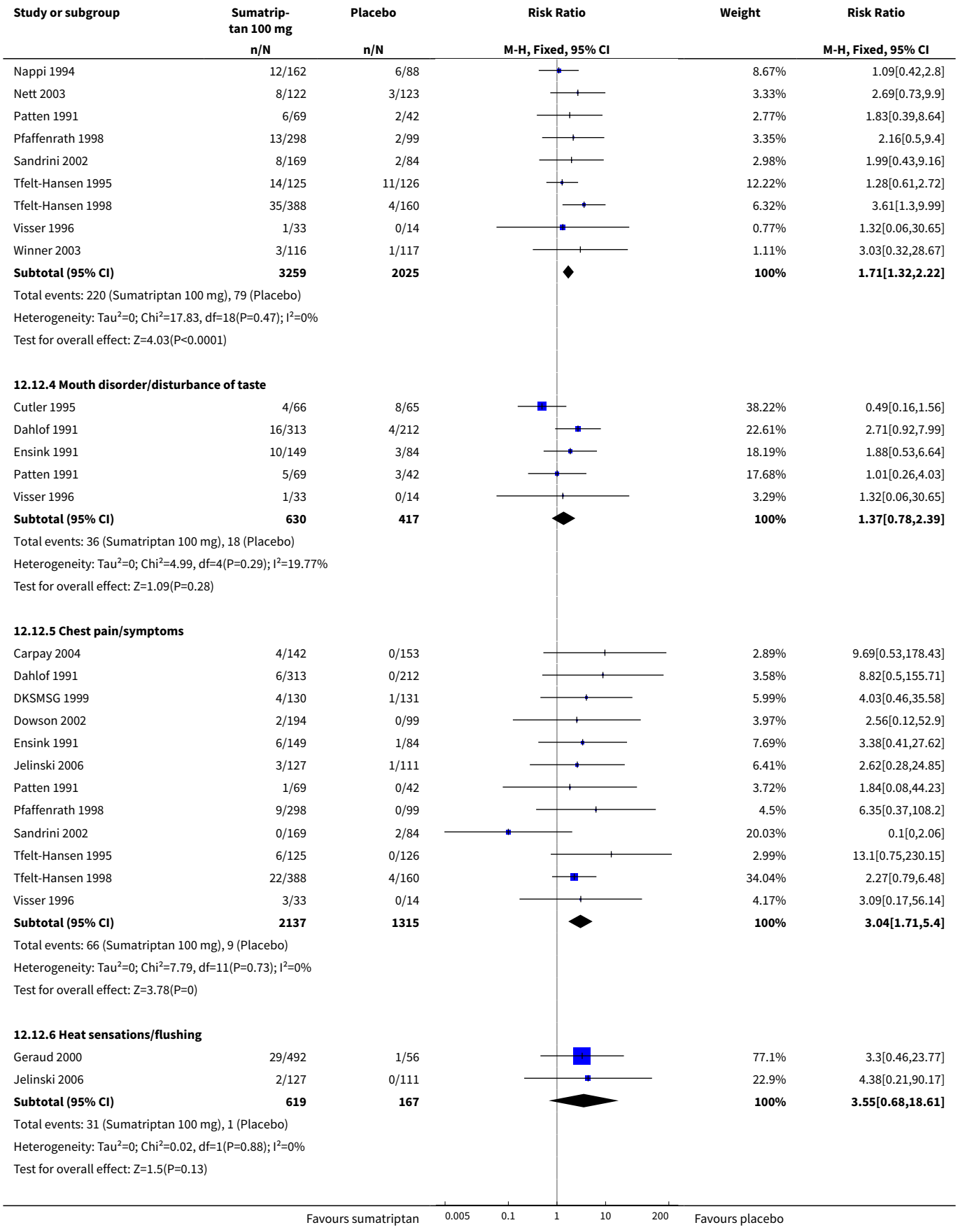
Study or subgroup	Sumatriptan 100 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
12.12.1 Malaise/fatigue/asthenia					
Carpay 2004	4/142	1/153		2.12%	4.31[0.49,38.1]
Dahlof 1991	19/313	4/212		10.49%	3.22[1.11,9.32]
DKSMSG 1999	7/130	4/131		8.76%	1.76[0.53,5.88]

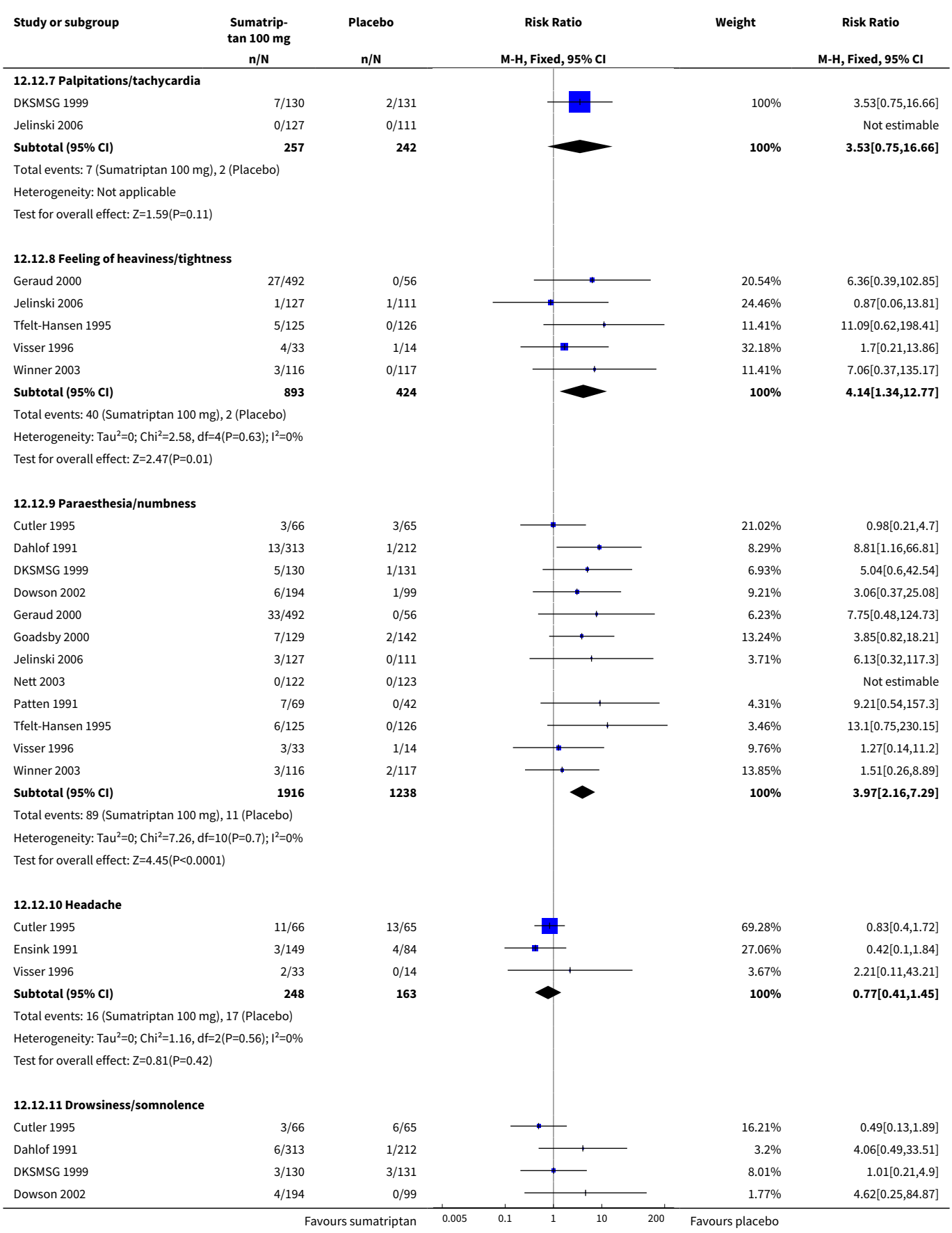


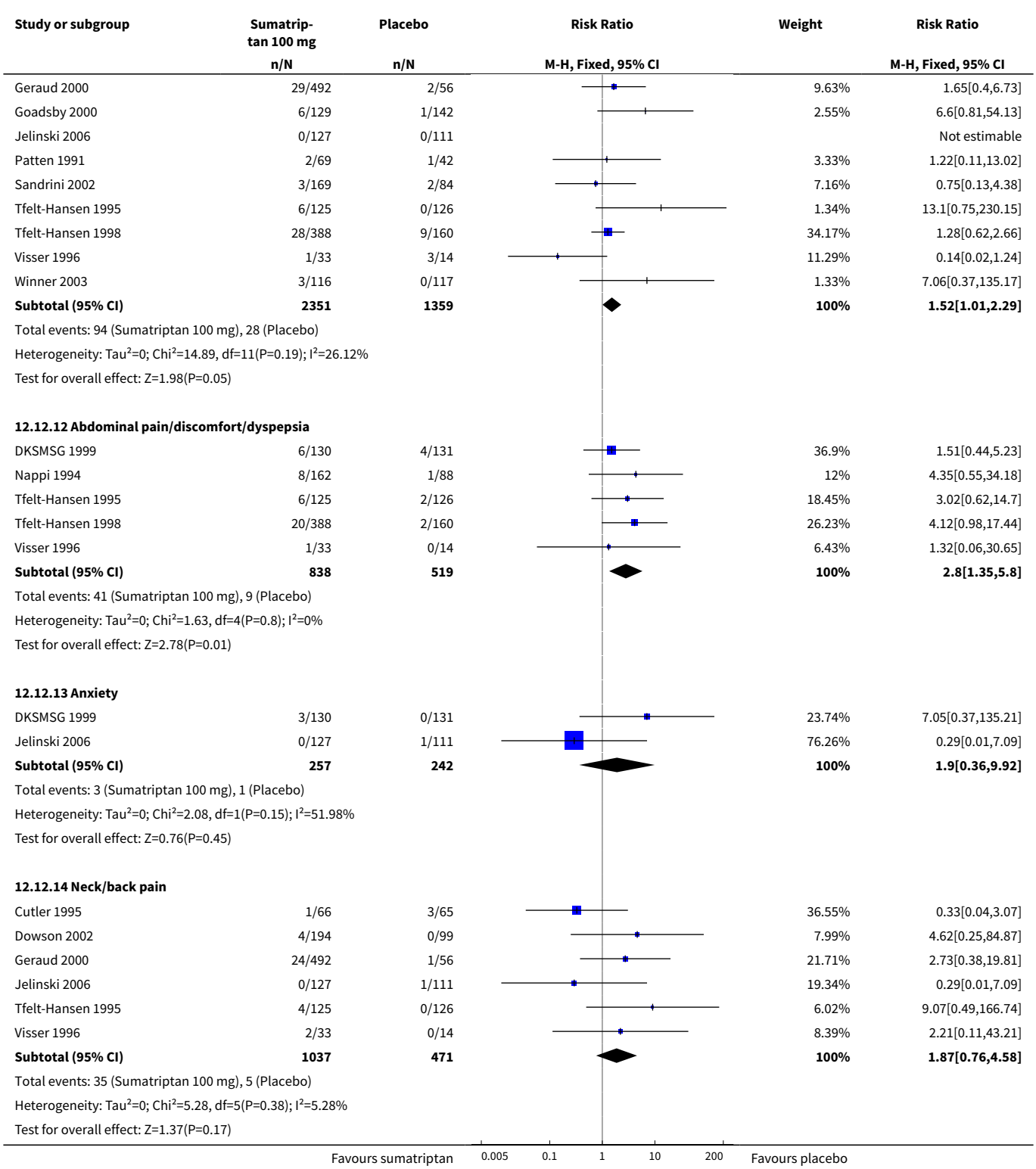
Favours sumatriptan — Favours placebo



Study or subgroup	Sumatriptan 100 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Dowson 2002	11/194	0/99		1.45%	11.79[0.7,198.11]
Ensink 1991	12/149	2/84		5.62%	3.38[0.78,14.75]
Geraud 2000	53/492	3/56		11.84%	2.01[0.65,6.22]
Goadsby 2000	4/129	0/142		1.05%	9.9[0.54,182.11]
Havanka 2000	4/98	5/91		11.4%	0.74[0.21,2.68]
Jelinski 2006	2/127	1/111		2.35%	1.75[0.16,19.02]
Nappi 1994	4/162	2/88		5.7%	1.09[0.2,5.81]
Nett 2003	0/122	1/123		3.28%	0.34[0.01,8.17]
Pfaffenrath 1998	15/298	1/99		3.3%	4.98[0.67,37.24]
Sandrini 2002	7/169	2/84		5.87%	1.74[0.37,8.19]
Tfelt-Hansen 1995	8/125	3/126		6.57%	2.69[0.73,9.9]
Tfelt-Hansen 1998	32/388	6/160		18.68%	2.2[0.94,5.16]
Visser 1996	1/33	0/14		1.53%	1.32[0.06,30.65]
Subtotal (95% CI)	**3071**	**1773**		**100%**	**2.36[1.64,3.38]**
Total events: 183 (Sumatriptan 100 mg), 35 (Placebo)					
Heterogeneity: Tau²=0; Chi²=9.64, df=15(P=0.84); I²=0%					
Test for overall effect: Z=4.66(P<0.0001)					
12.12.2 Dizziness/vertigo					
Cutler 1995	2/66	6/65		14.73%	0.33[0.07,1.57]
Dahlof 1991	19/313	2/212		5.81%	6.43[1.51,27.34]
DKSMSG 1999	7/130	3/131		7.28%	2.35[0.62,8.9]
Dowson 2002	4/194	2/99		6.45%	1.02[0.19,5.48]
Ensink 1991	7/149	2/84		6.23%	1.97[0.42,9.28]
Geraud 2000	46/492	1/56		4.37%	5.24[0.74,37.24]
Goadsby 2000	5/129	1/142		2.32%	5.5[0.65,46.49]
Jelinski 2006	4/127	2/111		5.2%	1.75[0.33,9.36]
Kaniecki 2006	5/131	0/127		1.24%	10.67[0.6,190.94]
Nett 2003	0/122	1/123		3.64%	0.34[0.01,8.17]
Pfaffenrath 1998	14/298	2/99		7.31%	2.33[0.54,10.05]
Sandrini 2002	5/169	2/84		6.51%	1.24[0.25,6.27]
Tfelt-Hansen 1995	3/125	1/126		2.43%	3.02[0.32,28.68]
Tfelt-Hansen 1998	35/388	6/160		20.7%	2.41[1.03,5.61]
Visser 1996	1/33	1/14		3.42%	0.42[0.03,6.32]
Winner 2003	5/223	1/237		2.36%	5.31[0.63,45.13]
Subtotal (95% CI)	**3089**	**1870**		**100%**	**2.34[1.6,3.42]**
Total events: 162 (Sumatriptan 100 mg), 33 (Placebo)					
Heterogeneity: Tau²=0; Chi²=15.52, df=15(P=0.41); I²=3.38%					
Test for overall effect: Z=4.36(P<0.0001)					
12.12.3 Nausea/vomiting					
Carpay 2004	7/142	3/153		3.22%	2.51[0.66,9.54]
Cutler 1995	10/66	16/65		17.98%	0.62[0.3,1.25]
Dahlof 1991	34/313	11/212		14.63%	2.09[1.09,4.04]
DKSMSG 1999	3/130	5/131		5.56%	0.6[0.15,2.48]
Ensink 1991	12/149	5/84		7.13%	1.35[0.49,3.71]
Geraud 2000	35/492	1/56		2%	3.98[0.56,28.52]
Goadsby 2000	4/129	1/142		1.06%	4.4[0.5,38.89]
Havanka 2000	1/98	1/91		1.16%	0.93[0.06,14.63]
Jelinski 2006	5/127	1/111		1.19%	4.37[0.52,36.84]
Kaniecki 2006	9/131	4/127		4.53%	2.18[0.69,6.9]







Analysis 12.13. Comparison 12 Oral sumatriptan 100 mg versus placebo, Outcome 13 Any adverse event withdrawal.

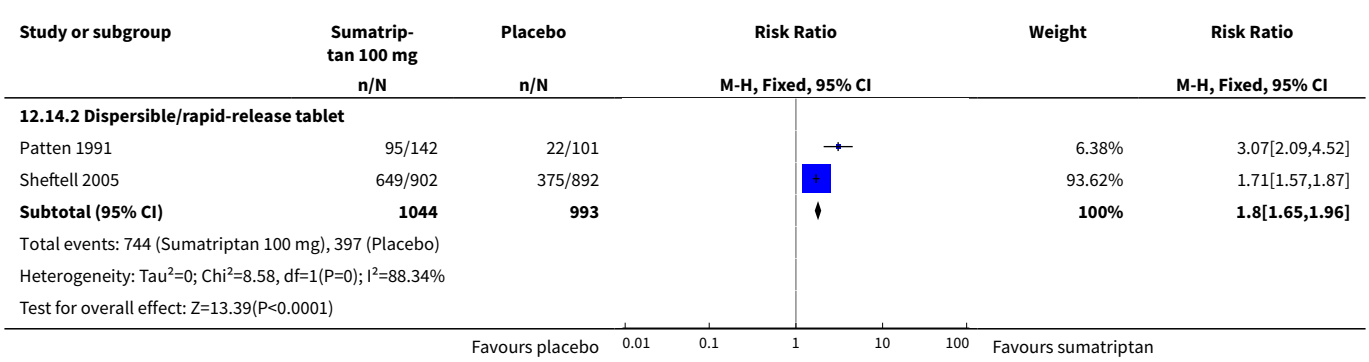
Study or subgroup	Sumatriptan 100 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Dahlof 1991	10/313	3/212		30.98%	2.26[0.63,8.11]
DKSMSG 1999	0/130	2/131		21.57%	0.2[0.01,4.16]
Dowson 2002	0/194	0/99			Not estimable
Ensink 1991	2/149	1/84		11.08%	1.13[0.1,12.25]
Havanka 2000	0/98	0/91			Not estimable
Pfaffenrath 1998	8/298	1/99		13%	2.66[0.34,20.99]
Tfelt-Hansen 1995	4/125	2/126		17.25%	2.02[0.38,10.81]
Tfelt-Hansen 1998	1/388	0/160		6.13%	1.24[0.05,30.32]
Visser 1996	0/33	0/14			Not estimable
Total (95% CI)	**1728**	**1016**		**100%**	**1.64[0.77,3.47]**
Total events: 25 (Sumatriptan 100 mg), 9 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.48, df=5(P=0.78); I^2=0%					
Test for overall effect: Z=1.28(P=0.2)					

Favours placebo — Favours sumatriptan

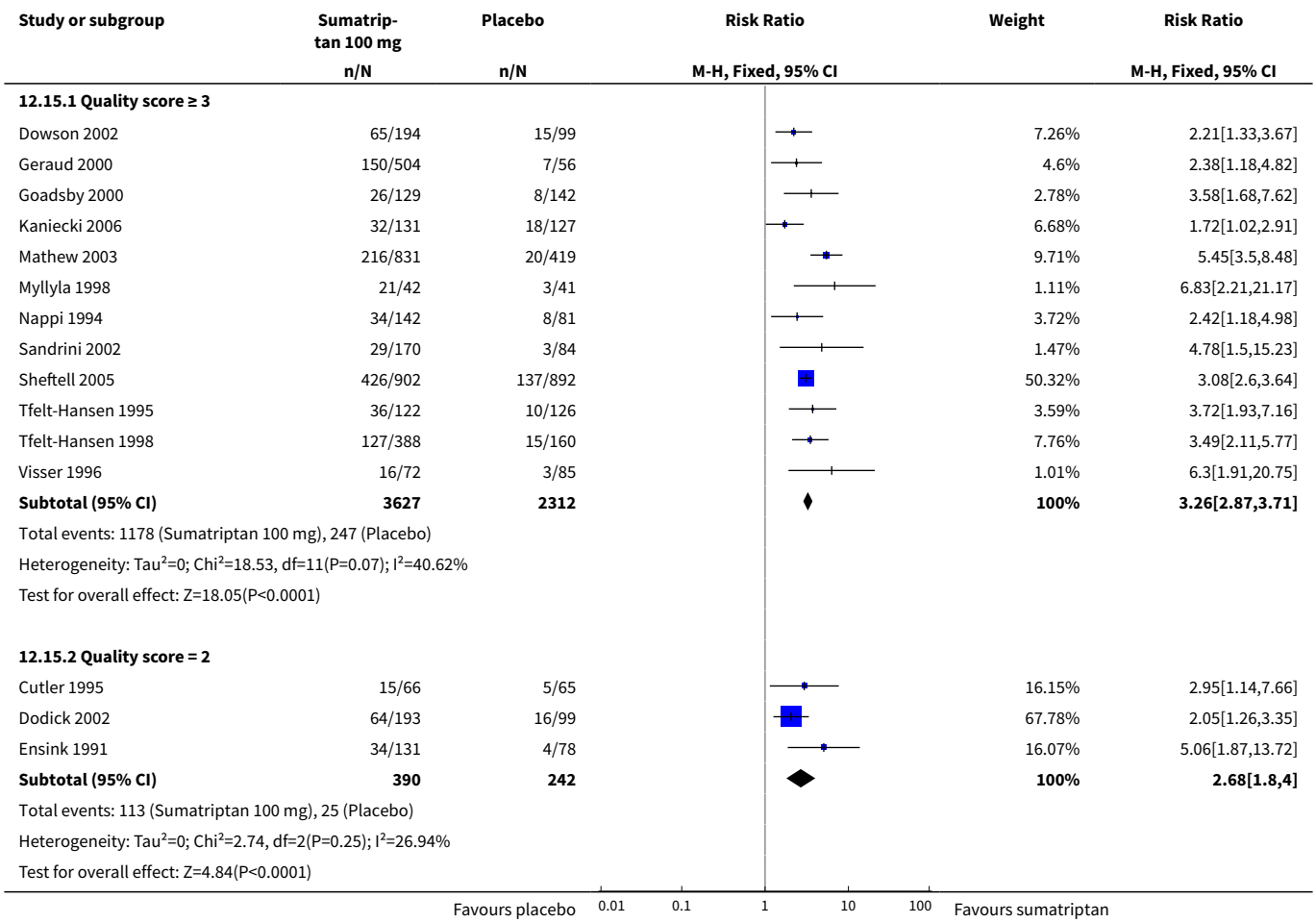
Analysis 12.14. Comparison 12 Oral sumatriptan 100 mg versus placebo, Outcome 14 Headache relief at 2 h - effect of formulation.

Study or subgroup	Sumatriptan 100 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
12.14.1 Standard tablet					
Cutler 1995	37/66	17/65		2.43%	2.14[1.35,3.4]
Dahlof 1991	180/275	48/182		8.2%	2.48[1.92,3.21]
Dowson 2002	123/194	42/99		7.89%	1.49[1.16,1.93]
Ensink 1991	60/131	14/78		2.49%	2.55[1.53,4.25]
Geraud 2000	304/504	24/56		6.13%	1.41[1.03,1.92]
Goadsby 1991	45/89	9/93		1.25%	5.22[2.72,10.05]
Goadsby 2000	63/129	30/142		4.05%	2.31[1.61,3.33]
Havanka 2000	59/98	28/91		4.12%	1.96[1.38,2.77]
Kaniecki 2006	64/131	47/127		6.77%	1.32[0.99,1.76]
Mathew 2003	471/831	105/419		19.81%	2.26[1.9,2.7]
Myllyla 1998	33/42	12/41		1.72%	2.68[1.63,4.43]
Nappi 1994	73/142	25/81		4.52%	1.67[1.16,2.39]
Pfaffenrath 1998	175/277	27/91		5.77%	2.13[1.53,2.96]
Sandrini 2002	85/170	25/84		4.75%	1.68[1.17,2.41]
Sargent 1995	26/46	8/47		1.12%	3.32[1.68,6.56]
Tfelt-Hansen 1995	63/122	30/126		4.19%	2.17[1.52,3.1]
Tfelt-Hansen 1998	239/388	64/160		12.86%	1.54[1.25,1.89]
Visser 1996	33/72	15/85		1.95%	2.6[1.54,4.38]
Subtotal (95% CI)	**3707**	**2067**		**100%**	**2[1.86,2.16]**
Total events: 2133 (Sumatriptan 100 mg), 570 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=45.38, df=17(P=0); I^2=62.54%					
Test for overall effect: Z=18.08(P<0.0001)					

Favours placebo — Favours sumatriptan

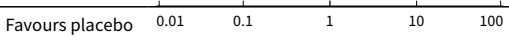


Analysis 12.15. Comparison 12 Oral sumatriptan 100 mg versus placebo, Outcome 15 Pain-free at 2 h - effect of quality score.



Analysis 12.16. Comparison 12 Oral sumatriptan 100 mg versus placebo, Outcome 16 Headache relief at 2 h - effect of quality score.

Study or subgroup	Sumatriptan 100 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
12.16.1 Quality score ≥ 3					
Dowson 2002	123/194	42/99		5.62%	1.49[1.16,1.93]
Geraud 2000	304/504	24/56		4.37%	1.41[1.03,1.92]
Goadsby 1991	45/89	9/93		0.89%	5.22[2.72,10.05]
Goadsby 2000	63/129	30/142		2.89%	2.31[1.61,3.33]
Havanka 2000	59/98	28/91		2.93%	1.96[1.38,2.77]
Kaniecki 2006	64/131	47/127		4.82%	1.32[0.99,1.76]
Mathew 2003	471/831	105/419		14.11%	2.26[1.9,2.7]
Myllyla 1998	33/42	12/41		1.23%	2.68[1.63,4.43]
Nappi 1994	73/142	25/81		3.22%	1.67[1.16,2.39]
Pfaffenrath 1998	175/277	27/91		4.11%	2.13[1.53,2.96]
Sandrini 2002	85/170	25/84		3.38%	1.68[1.17,2.41]
Sargent 1995	26/46	8/47		0.8%	3.32[1.68,6.56]
Sheftell 2005	649/902	375/892		38.11%	1.71[1.57,1.87]
Tfelt-Hansen 1995	63/122	30/126		2.98%	2.17[1.52,3.1]
Tfelt-Hansen 1998	239/388	64/160		9.16%	1.54[1.25,1.89]
Visser 1996	33/72	15/85		1.39%	2.6[1.54,4.38]
Subtotal (95% CI)	**4137**	**2634**		**100%**	**1.85[1.74,1.97]**
Total events: 2505 (Sumatriptan 100 mg), 866 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=42.03, df=15(P=0); I^2=64.31%					
Test for overall effect: Z=20(P<0.0001)					
12.16.2 Quality score = 2					
Cutler 1995	37/66	17/65		14.5%	2.14[1.35,3.4]
Dahlof 1991	180/275	48/182		48.89%	2.48[1.92,3.21]
Ensink 1991	60/131	14/78		14.85%	2.55[1.53,4.25]
Patten 1991	95/142	22/101		21.76%	3.07[2.09,4.52]
Subtotal (95% CI)	**614**	**426**		**100%**	**2.57[2.14,3.09]**
Total events: 372 (Sumatriptan 100 mg), 101 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.48, df=3(P=0.69); I^2=0%					
Test for overall effect: Z=10.16(P<0.0001)					



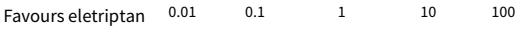
Comparison 13. Oral sumatriptan 100 mg versus eletriptan 40 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain-free at 2 h	3	2263	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.65, 0.85]
2 Pain-free at 1 h	3	2263	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.57, 1.10]
3 Headache relief at 1 h	3	2263	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.67, 0.88]
4 Headache relief at 2 h	3	2263	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.82, 0.95]
5 24 h sustained headache relief	2	1998	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.70, 0.88]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Use of rescue medication	2	1918	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [1.10, 1.51]
6.1 Up to 24 h after initial dosing	2	1918	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [1.10, 1.51]
7 Relief of associated symptoms	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Relief of nausea at 2 h	3	1478	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.79, 0.96]
7.2 Relief of photophobia at 2 h	3	1692	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.78, 0.93]
7.3 Relief of phonophobia at 2 h	2	1361	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.76, 0.92]
8 Relief of functional disability at 2 h	3	1880	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.81, 0.92]

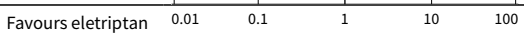
Analysis 13.1. Comparison 13 Oral sumatriptan 100 mg versus eletriptan 40 mg, Outcome 1 Pain-free at 2 h.

Study or subgroup	Sumatriptan 100 mg n/N	Eletriptan 40 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Goadsby 2000	26/129	34/136		9.05%	0.81[0.51,1.26]
Mathew 2003	216/831	280/822		76.95%	0.76[0.66,0.89]
Sandrini 2002	29/170	52/175		14.01%	0.57[0.38,0.86]
Total (95% CI)	**1130**	**1133**		**100%**	**0.74[0.65,0.85]**
Total events: 271 (Sumatriptan 100 mg), 366 (Eletriptan 40 mg)					
Heterogeneity: Tau^2=0; Chi^2=1.83, df=2(P=0.4); I^2=0%					
Test for overall effect: Z=4.41(P<0.0001)					



Analysis 13.2. Comparison 13 Oral sumatriptan 100 mg versus eletriptan 40 mg, Outcome 2 Pain-free at 1 h.

Study or subgroup	Sumatriptan 100 mg n/N	Eletriptan 40 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Goadsby 2000	7/129	9/136		11.7%	0.82[0.31,2.14]
Mathew 2003	40/831	56/822		75.15%	0.71[0.48,1.05]
Sandrini 2002	12/170	10/175		13.15%	1.24[0.55,2.78]
Total (95% CI)	**1130**	**1133**		**100%**	**0.79[0.57,1.1]**
Total events: 59 (Sumatriptan 100 mg), 75 (Eletriptan 40 mg)					
Heterogeneity: Tau^2=0; Chi^2=1.48, df=2(P=0.48); I^2=0%					
Test for overall effect: Z=1.4(P=0.16)					



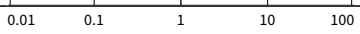
Analysis 13.3. Comparison 13 Oral sumatriptan 100 mg versus eletriptan 40 mg, Outcome 3 Headache relief at 1 h.

Study or subgroup	Sumatriptan 100 mg n/N	Eletriptan 40 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Goadsby 2000	23/129	44/136		11.65%	0.55[0.35,0.86]
Mathew 2003	214/831	272/822		74.4%	0.78[0.67,0.91]
Sandrini 2002	45/170	52/175		13.94%	0.89[0.63,1.25]
Total (95% CI)	**1130**	**1133**		**100%**	**0.77[0.67,0.88]**
Total events: 282 (Sumatriptan 100 mg), 368 (Eletriptan 40 mg)					
Heterogeneity: Tau^2=0; Chi^2=2.92, df=2(P=0.23); I^2=31.59%					
Test for overall effect: Z=3.95(P<0.0001)					

Favours eletriptan — Favours sumatriptan

Analysis 13.4. Comparison 13 Oral sumatriptan 100 mg versus eletriptan 40 mg, Outcome 4 Headache relief at 2 h.

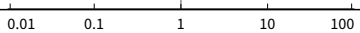
Study or subgroup	Sumatriptan 100 mg n/N	Eletriptan 40 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Goadsby 2000	66/129	76/136		10.49%	0.92[0.73,1.15]
Mathew 2003	471/831	522/822		74.42%	0.89[0.82,0.97]
Sandrini 2002	85/170	108/175		15.09%	0.81[0.67,0.98]
Total (95% CI)	**1130**	**1133**		**100%**	**0.88[0.82,0.95]**
Total events: 622 (Sumatriptan 100 mg), 706 (Eletriptan 40 mg)					
Heterogeneity: Tau^2=0; Chi^2=0.96, df=2(P=0.62); I^2=0%					
Test for overall effect: Z=3.53(P=0)					



Favours eletriptan — Favours sumatriptan

Analysis 13.5. Comparison 13 Oral sumatriptan 100 mg versus eletriptan 40 mg, Outcome 5 24 h sustained headache relief.

Study or subgroup	Sumatriptan 100 mg n/N	Eletriptan 40 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Mathew 2003	276/831	342/822		79.86%	0.8[0.7,0.91]
Sandrini 2002	64/170	88/175		20.14%	0.75[0.59,0.95]
Total (95% CI)	**1001**	**997**		**100%**	**0.79[0.7,0.88]**
Total events: 340 (Sumatriptan 100 mg), 430 (Eletriptan 40 mg)					
Heterogeneity: Tau^2=0; Chi^2=0.21, df=1(P=0.65); I^2=0%					
Test for overall effect: Z=4.17(P<0.0001)					



Favours eletriptan — Favours sumatriptan

Analysis 13.6. Comparison 13 Oral sumatriptan 100 mg versus eletriptan 40 mg, Outcome 6 Use of rescue medication.

Study or subgroup	Sumatriptan 100 mg n/N	Eletriptan 40 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
13.6.1 Up to 24 h after initial dosing					
Goadsby 2000	37/129	39/136		18.72%	1[0.68,1.46]
Mathew 2003	224/831	164/822		81.28%	1.35[1.13,1.61]
Subtotal (95% CI)	**960**	**958**		**100%**	**1.29[1.1,1.51]**
Total events: 261 (Sumatriptan 100 mg), 203 (Eletriptan 40 mg)					
Heterogeneity: Tau^2=0; Chi^2=1.98, df=1(P=0.16); I^2=49.5%					
Test for overall effect: Z=3.07(P=0)					
Total (95% CI)	**960**	**958**		**100%**	**1.29[1.1,1.51]**
Total events: 261 (Sumatriptan 100 mg), 203 (Eletriptan 40 mg)					
Heterogeneity: Tau^2=0; Chi^2=1.98, df=1(P=0.16); I^2=49.5%					
Test for overall effect: Z=3.07(P=0)					

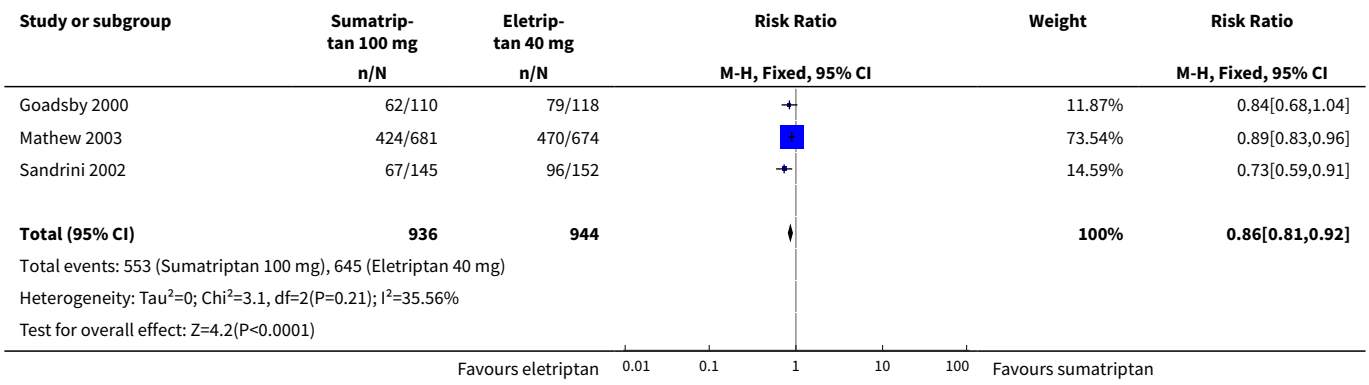
Favours sumatriptan — Favours eletriptan

Analysis 13.7. Comparison 13 Oral sumatriptan 100 mg versus eletriptan 40 mg, Outcome 7 Relief of associated symptoms.

Study or subgroup	Sumatriptan 100 mg n/N	Eletriptan 40 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
13.7.1 Relief of nausea at 2 h					
Goadsby 2000	44/82	47/136		8.57%	1.55[1.14,2.11]
Mathew 2003	252/515	308/510		75.06%	0.81[0.72,0.91]
Sandrini 2002	56/122	65/113		16.37%	0.8[0.62,1.02]
Subtotal (95% CI)	**719**	**759**		**100%**	**0.87[0.79,0.96]**
Total events: 352 (Sumatriptan 100 mg), 420 (Eletriptan 40 mg)					
Heterogeneity: Tau^2=0; Chi^2=15.72, df=2(P=0); I^2=87.28%					
Test for overall effect: Z=2.77(P=0.01)					
13.7.2 Relief of photophobia at 2 h					
Goadsby 2000	58/107	63/107		12.45%	0.92[0.73,1.16]
Mathew 2003	328/623	366/592		74.2%	0.85[0.77,0.94]
Sandrini 2002	52/125	71/138		13.34%	0.81[0.62,1.05]
Subtotal (95% CI)	**855**	**837**		**100%**	**0.85[0.78,0.93]**
Total events: 438 (Sumatriptan 100 mg), 500 (Eletriptan 40 mg)					
Heterogeneity: Tau^2=0; Chi^2=0.56, df=2(P=0.76); I^2=0%					
Test for overall effect: Z=3.6(P=0)					
13.7.3 Relief of phonophobia at 2 h					
Mathew 2003	294/557	325/526		81.25%	0.85[0.77,0.95]
Sandrini 2002	58/134	80/144		18.75%	0.78[0.61,0.99]
Subtotal (95% CI)	**691**	**670**		**100%**	**0.84[0.76,0.92]**
Total events: 352 (Sumatriptan 100 mg), 405 (Eletriptan 40 mg)					
Heterogeneity: Tau^2=0; Chi^2=0.47, df=1(P=0.49); I^2=0%					
Test for overall effect: Z=3.58(P=0)					

Favours eletriptan — Favours sumatriptan

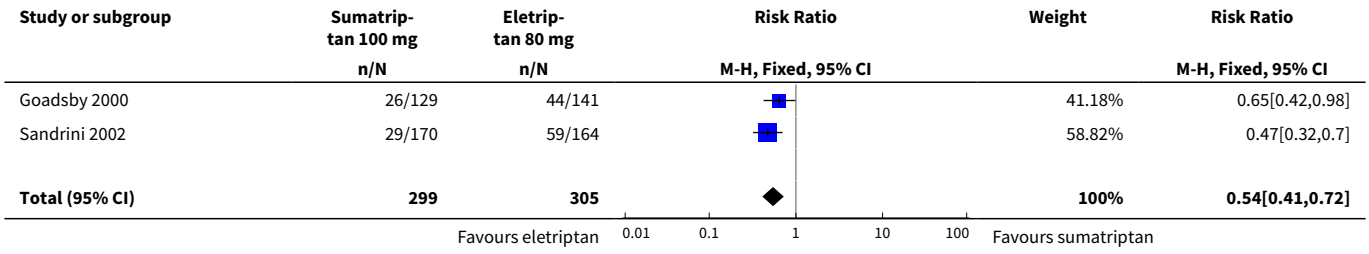
Analysis 13.8. Comparison 13 Oral sumatriptan 100 mg versus eletriptan 40 mg, Outcome 8 Relief of functional disability at 2 h.



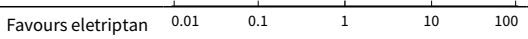
Comparison 14. Oral sumatriptan 100 mg versus eletriptan 80 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain-free at 2 h	2	604	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.41, 0.72]
2 Pain-free at 1 h	2	604	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.29, 0.82]
3 Headache relief at 1 h	2	604	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.50, 0.84]
4 Headache relief at 2 h	2	604	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.68, 0.89]
5 Relief of associated symptoms	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Relief of nausea at 2 h	2	408	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.69, 0.99]
5.2 Relief of photophobia at 2 h	2	457	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.64, 0.89]
6 Relief of functional disability at 2 h	2	516	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.67, 0.90]

Analysis 14.1. Comparison 14 Oral sumatriptan 100 mg versus eletriptan 80 mg, Outcome 1 Pain-free at 2 h.

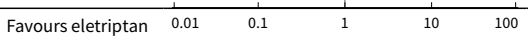


Study or subgroup	Sumatriptan 100 mg n/N	Eletriptan 80 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Total events: 55 (Sumatriptan 100 mg), 103 (Eletriptan 80 mg)					
Heterogeneity: Tau²=0; Chi²=1.11, df=1(P=0.29); I²=10.2%					
Test for overall effect: Z=4.17(P<0.0001)					



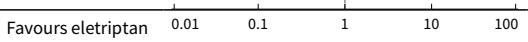
Analysis 14.2. Comparison 14 Oral sumatriptan 100 mg versus eletriptan 80 mg, Outcome 2 Pain-free at 1 h.

Study or subgroup	Sumatriptan 100 mg n/N	Eletriptan 80 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Goadsby 2000	7/129	20/141		48.42%	0.38[0.17,0.87]
Sandrini 2002	12/170	20/164		51.58%	0.58[0.29,1.15]
Total (95% CI)	**299**	**305**		**100%**	**0.48[0.29,0.82]**
Total events: 19 (Sumatriptan 100 mg), 40 (Eletriptan 80 mg)					
Heterogeneity: Tau²=0; Chi²=0.57, df=1(P=0.45); I²=0%					
Test for overall effect: Z=2.71(P=0.01)					



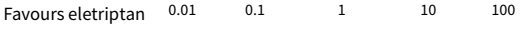
Analysis 14.3. Comparison 14 Oral sumatriptan 100 mg versus eletriptan 80 mg, Outcome 3 Headache relief at 1 h.

Study or subgroup	Sumatriptan 100 mg n/N	Eletriptan 80 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Goadsby 2000	23/129	48/141		43.72%	0.52[0.34,0.81]
Sandrini 2002	45/170	58/164		56.28%	0.75[0.54,1.04]
Total (95% CI)	**299**	**305**		**100%**	**0.65[0.5,0.84]**
Total events: 68 (Sumatriptan 100 mg), 106 (Eletriptan 80 mg)					
Heterogeneity: Tau²=0; Chi²=1.67, df=1(P=0.2); I²=40%					
Test for overall effect: Z=3.24(P=0)					

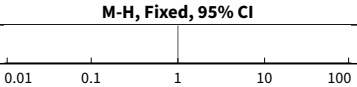


Analysis 14.4. Comparison 14 Oral sumatriptan 100 mg versus eletriptan 80 mg, Outcome 4 Headache relief at 2 h.

Study or subgroup	Sumatriptan 100 mg n/N	Eletriptan 80 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Goadsby 2000	66/129	91/141		44.39%	0.79[0.64,0.98]
Sandrini 2002	85/170	107/164		55.61%	0.77[0.64,0.92]
Total (95% CI)	**299**	**305**		**100%**	**0.78[0.68,0.89]**
Total events: 151 (Sumatriptan 100 mg), 198 (Eletriptan 80 mg)					
Heterogeneity: Tau²=0; Chi²=0.06, df=1(P=0.81); I²=0%					



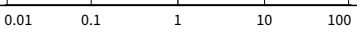
Study or subgroup	Sumatriptan 100 mg n/N	Eletriptan 80 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for overall effect: Z=3.53(P=0)					



Favours eletriptan — Favours sumatriptan

Analysis 14.5. Comparison 14 Oral sumatriptan 100 mg versus eletriptan 80 mg, Outcome 5 Relief of associated symptoms.

Study or subgroup	Sumatriptan 100 mg n/N	Eletriptan 80 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
14.5.1 Relief of nausea at 2 h					
Goadsby 2000	44/82	69/95		52.85%	0.74[0.58,0.94]
Sandrini 2002	56/122	54/109		47.15%	0.93[0.71,1.21]
Subtotal (95% CI)	**204**	**204**		**100%**	**0.83[0.69,0.99]**
Total events: 100 (Sumatriptan 100 mg), 123 (Eletriptan 80 mg)					
Heterogeneity: Tau^2=0; Chi^2=1.56, df=1(P=0.21); I^2=35.84%					
Test for overall effect: Z=2.07(P=0.04)					
14.5.2 Relief of photophobia at 2 h					
Goadsby 2000	58/107	75/109		51.67%	0.79[0.64,0.98]
Sandrini 2002	52/125	67/116		48.33%	0.72[0.56,0.93]
Subtotal (95% CI)	**232**	**225**		**100%**	**0.76[0.64,0.89]**
Total events: 110 (Sumatriptan 100 mg), 142 (Eletriptan 80 mg)					
Heterogeneity: Tau^2=0; Chi^2=0.28, df=1(P=0.6); I^2=0%					
Test for overall effect: Z=3.3(P=0)					



Favours eletriptan — Favours sumatriptan

Analysis 14.6. Comparison 14 Oral sumatriptan 100 mg versus eletriptan 80 mg, Outcome 6 Relief of functional disability at 2 h.

Study or subgroup	Sumatriptan 100 mg n/N	Eletriptan 80 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Goadsby 2000	62/110	98/125		54.24%	0.72[0.6,0.87]
Sandrini 2002	67/145	75/136		45.76%	0.84[0.66,1.06]
Total (95% CI)	**255**	**261**		**100%**	**0.77[0.67,0.9]**
Total events: 129 (Sumatriptan 100 mg), 173 (Eletriptan 80 mg)					
Heterogeneity: Tau^2=0; Chi^2=1.03, df=1(P=0.31); I^2=3.37%					
Test for overall effect: Z=3.4(P=0)					

Favours eletriptan — Favours sumatriptan

Comparison 15. Oral sumatriptan 100 mg versus rizatriptan 10 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain-free at 2 h	2	936	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.69, 0.98]
2 Headache relief at 1 h	2	936	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.62, 0.92]
3 Any adverse event within 24 h	2	856	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.96, 1.27]

Analysis 15.1. Comparison 15 Oral sumatriptan 100 mg versus rizatriptan 10 mg, Outcome 1 Pain-free at 2 h.

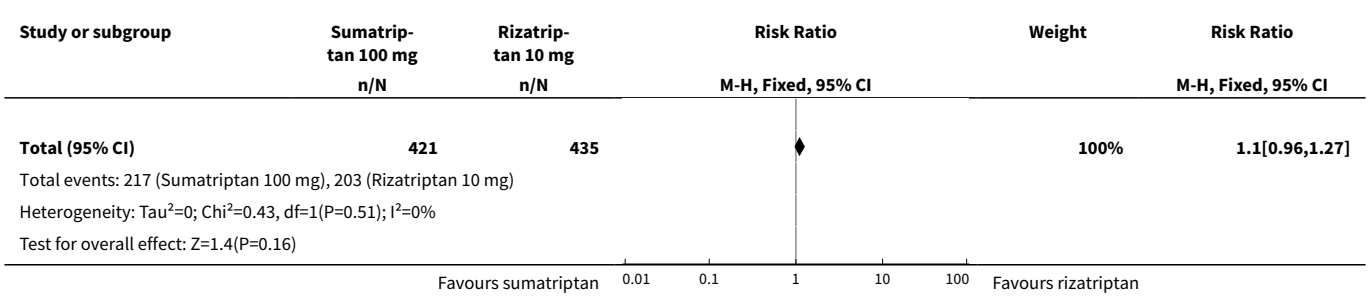
Study or subgroup	Sumatriptan 100 mg n/N	Rizatriptan 10 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Tfelt-Hansen 1998	127/388	155/387		88.3%	0.82[0.68,0.99]
Visser 1996	16/72	23/89		11.7%	0.86[0.49,1.5]
Total (95% CI)	**460**	**476**		**100%**	**0.82[0.69,0.98]**
Total events: 143 (Sumatriptan 100 mg), 178 (Rizatriptan 10 mg)					
Heterogeneity: Tau^2=0; Chi^2=0.03, df=1(P=0.87); I^2=0%					
Test for overall effect: Z=2.15(P=0.03)					

Analysis 15.2. Comparison 15 Oral sumatriptan 100 mg versus rizatriptan 10 mg, Outcome 2 Headache relief at 1 h.

Study or subgroup	Sumatriptan 100 mg n/N	Rizatriptan 10 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Tfelt-Hansen 1998	103/388	141/387		87.77%	0.73[0.59,0.9]
Visser 1996	17/72	22/89		12.23%	0.96[0.55,1.66]
Total (95% CI)	**460**	**476**		**100%**	**0.76[0.62,0.92]**
Total events: 120 (Sumatriptan 100 mg), 163 (Rizatriptan 10 mg)					
Heterogeneity: Tau^2=0; Chi^2=0.81, df=1(P=0.37); I^2=0%					
Test for overall effect: Z=2.77(P=0.01)					

Analysis 15.3. Comparison 15 Oral sumatriptan 100 mg versus rizatriptan 10 mg, Outcome 3 Any adverse event within 24 h.

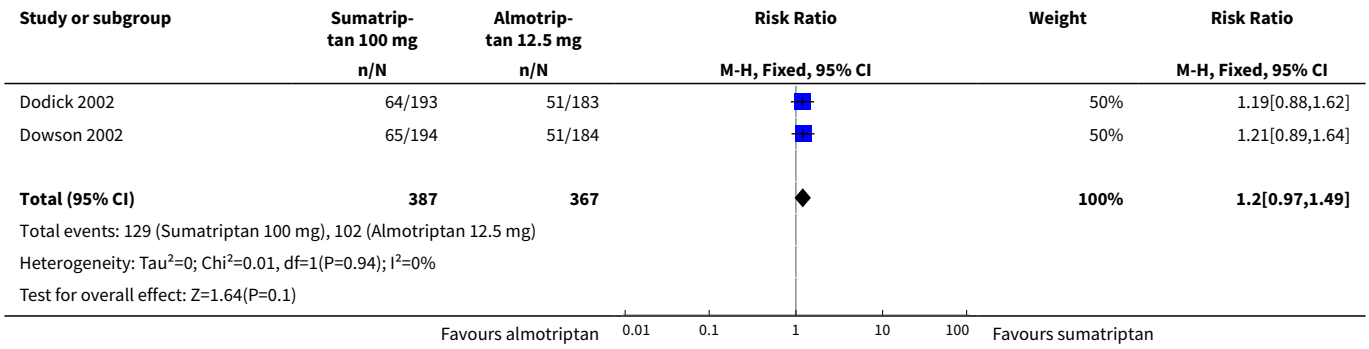
Study or subgroup	Sumatriptan 100 mg n/N	Rizatriptan 10 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Tfelt-Hansen 1998	202/388	180/387		90.58%	1.12[0.97,1.29]
Visser 1996	15/33	23/48		9.42%	0.95[0.59,1.53]



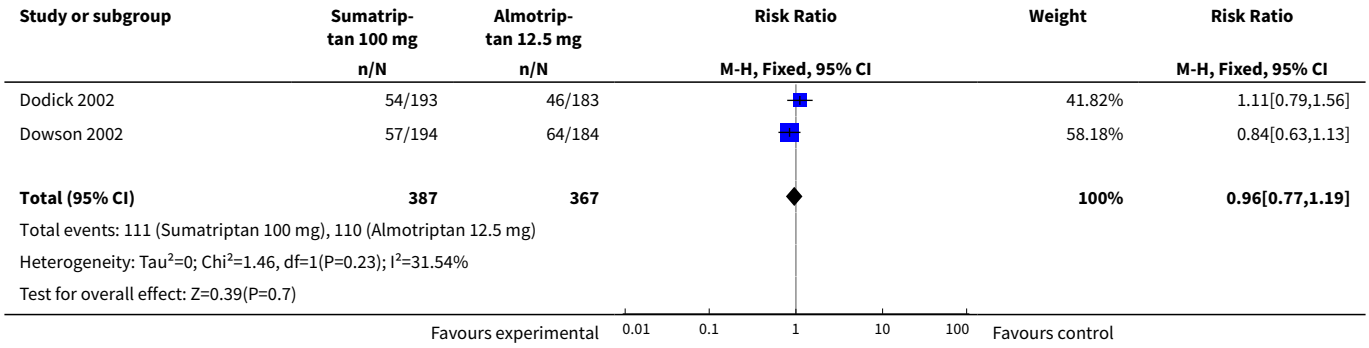
Comparison 16. Oral sumatriptan 100 mg versus almotriptan 12.5 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain-free at 2 h	2	754	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.97, 1.49]
2 24 h sustained pain-free	2	754	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.77, 1.19]

Analysis 16.1. Comparison 16 Oral sumatriptan 100 mg versus almotriptan 12.5 mg, Outcome 1 Pain-free at 2 h.



Analysis 16.2. Comparison 16 Oral sumatriptan 100 mg versus almotriptan 12.5 mg, Outcome 2 24 h sustained pain-free.

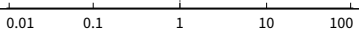


Comparison 17. Oral sumatriptan 100 mg versus paracetamol 1000 mg + metoclopramide 10 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Headache relief at 2 hours	2	1035	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.91, 1.20]
2 Relief of associated symptoms	2	1001	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.83, 1.18]
2.1 Relief of photophobia or phonophobia	2	1001	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.83, 1.18]
3 Use of rescue medication	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Up to 24 h after initial dosing	2	1243	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.74, 0.99]
4 Any adverse event within 24 h	2	1328	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [1.42, 1.89]

Analysis 17.1. Comparison 17 Oral sumatriptan 100 mg versus paracetamol 1000 mg + metoclopramide 10 mg, Outcome 1 Headache relief at 2 hours.

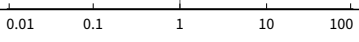
Study or subgroup	Sumatriptan 100 mg n/N	Paracetamol + MCP n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
GL/MIG/001/92	118/242	103/227		47.55%	1.07[0.89,1.3]
GL/MIG/001A/92	115/272	122/294		52.45%	1.02[0.84,1.24]
Total (95% CI)	**514**	**521**		**100%**	**1.05[0.91,1.2]**
Total events: 233 (Sumatriptan 100 mg), 225 (Paracetamol + MCP)					
Heterogeneity: Tau^2=0; Chi^2=0.15, df=1(P=0.7); I^2=0%					
Test for overall effect: Z=0.64(P=0.52)					



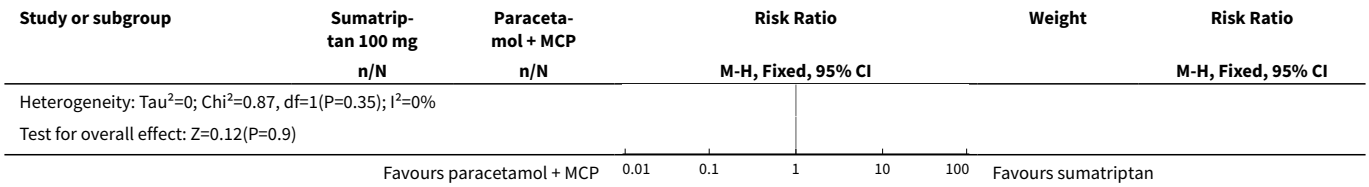
Favours paracetamol + MCP — Favours sumatriptan

Analysis 17.2. Comparison 17 Oral sumatriptan 100 mg versus paracetamol 1000 mg + metoclopramide 10 mg, Outcome 2 Relief of associated symptoms.

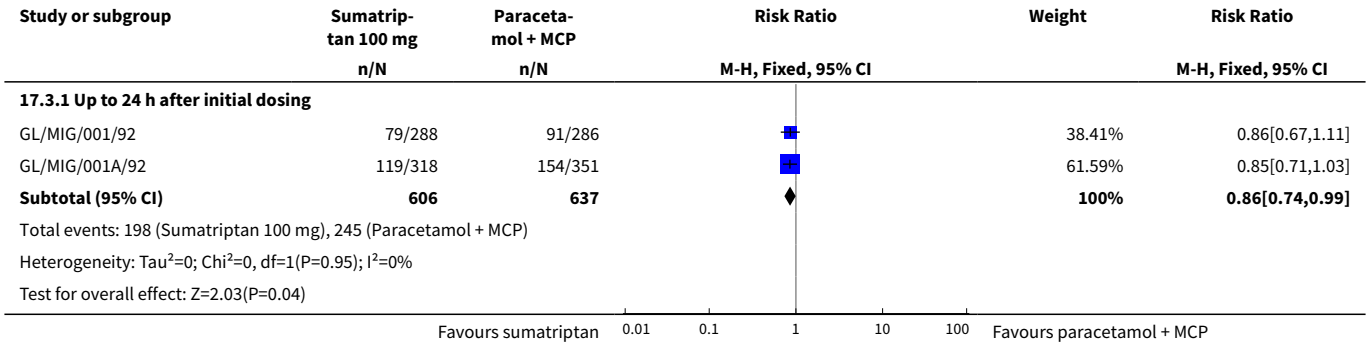
Study or subgroup	Sumatriptan 100 mg n/N	Paracetamol + MCP n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
17.2.1 Relief of photophobia or phonophobia					
GL/MIG/001/92	79/234	85/229		52.99%	0.91[0.71,1.16]
GL/MIG/001A/92	76/247	83/291		47.01%	1.08[0.83,1.4]
Subtotal (95% CI)	**481**	**520**		**100%**	**0.99[0.83,1.18]**
Total events: 155 (Sumatriptan 100 mg), 168 (Paracetamol + MCP)					
Heterogeneity: Tau^2=0; Chi^2=0.87, df=1(P=0.35); I^2=0%					
Test for overall effect: Z=0.12(P=0.9)					
Total (95% CI)	**481**	**520**		**100%**	**0.99[0.83,1.18]**
Total events: 155 (Sumatriptan 100 mg), 168 (Paracetamol + MCP)					



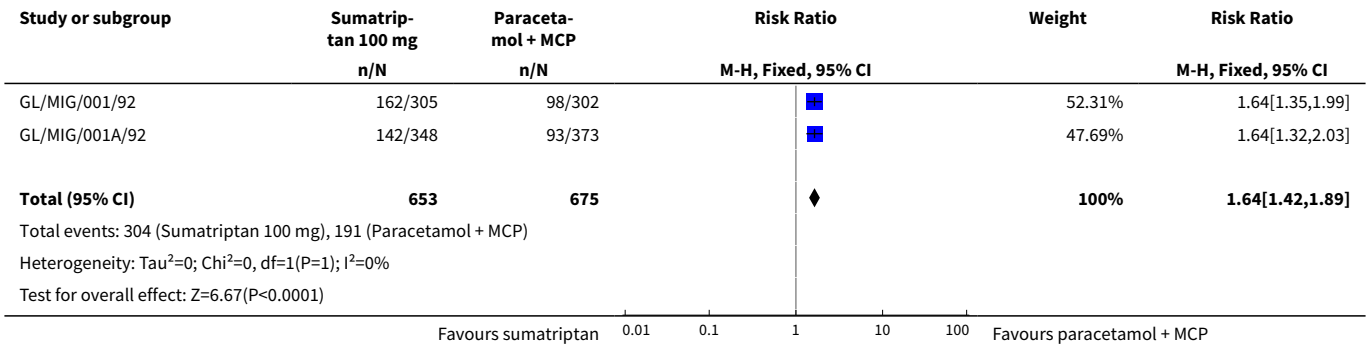
Favours paracetamol + MCP — Favours sumatriptan



Analysis 17.3. Comparison 17 Oral sumatriptan 100 mg versus paracetamol 1000 mg + metoclopramide 10 mg, Outcome 3 Use of rescue medication.



Analysis 17.4. Comparison 17 Oral sumatriptan 100 mg versus paracetamol 1000 mg + metoclopramide 10 mg, Outcome 4 Any adverse event within 24 h.



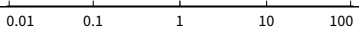
Comparison 18. Oral sumatriptan 100 mg versus acetylsalicylic acid 900 mg + metoclopramide 10 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain-free at 2 hours	2	575	Risk Ratio (M-H, Fixed, 95% CI)	1.62 [1.17, 2.25]
2 Headache relief at 2 hours	2	575	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.92, 1.29]
3 Relief of associated symptoms	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Relief of nausea at 2 hours	2	410	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.69, 1.20]
4 Any adverse event within 24 hours	2	621	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [1.20, 1.94]

Analysis 18.1. Comparison 18 Oral sumatriptan 100 mg versus acetylsalicylic acid 900 mg + metoclopramide 10 mg, Outcome 1 Pain-free at 2 hours.

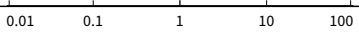
Study or subgroup	Sumatriptan 100 mg n/N	ASA 900 mg + MCP 10 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Tfelt-Hansen 1995	36/122	29/137		59.76%	1.39[0.91,2.13]
Thomson 1992	35/153	19/163		40.24%	1.96[1.17,3.28]
Total (95% CI)	**275**	**300**		**100%**	**1.62[1.17,2.25]**
Total events: 71 (Sumatriptan 100 mg), 48 (ASA 900 mg + MCP 10 mg)					
Heterogeneity: Tau^2=0; Chi^2=1.02, df=1(P=0.31); I^2=2.06%					
Test for overall effect: Z=2.91(P=0)					



Favours ASA + MCP — Favours sumatriptan

Analysis 18.2. Comparison 18 Oral sumatriptan 100 mg versus acetylsalicylic acid 900 mg + metoclopramide 10 mg, Outcome 2 Headache relief at 2 hours.

Study or subgroup	Sumatriptan 100 mg n/N	ASA 900 mg + MCP 10 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Tfelt-Hansen 1995	63/122	76/137		54.39%	0.93[0.74,1.17]
Thomson 1992	74/153	62/163		45.61%	1.27[0.99,1.64]
Total (95% CI)	**275**	**300**		**100%**	**1.09[0.92,1.29]**
Total events: 137 (Sumatriptan 100 mg), 138 (ASA 900 mg + MCP 10 mg)					
Heterogeneity: Tau^2=0; Chi^2=3.22, df=1(P=0.07); I^2=68.97%					
Test for overall effect: Z=0.95(P=0.34)					

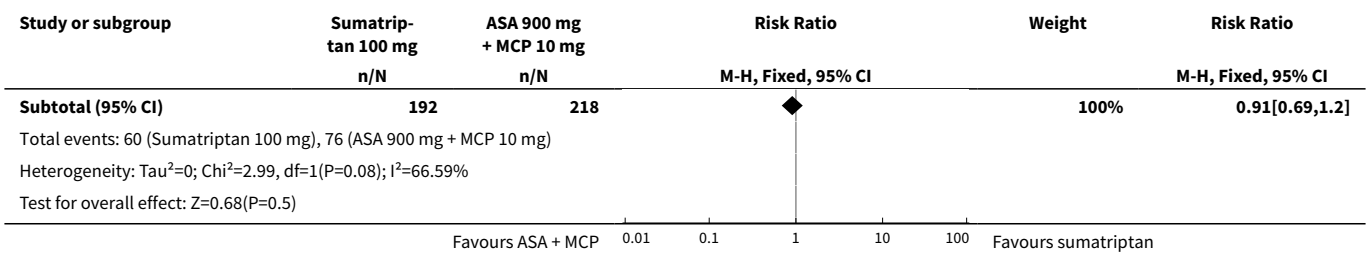


Favours ASA + MCP — Favours sumatriptan

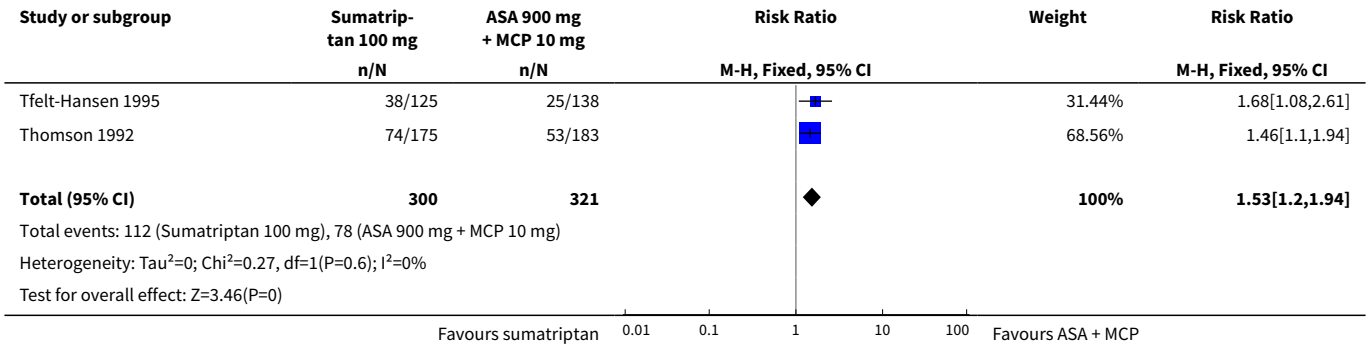
Analysis 18.3. Comparison 18 Oral sumatriptan 100 mg versus acetylsalicylic acid 900 mg + metoclopramide 10 mg, Outcome 3 Relief of associated symptoms.

Study or subgroup	Sumatriptan 100 mg n/N	ASA 900 mg + MCP 10 mg n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
18.3.1 Relief of nausea at 2 hours					
Tfelt-Hansen 1995	26/84	46/106		58%	0.71[0.48,1.05]
Thomson 1992	34/108	30/112		42%	1.18[0.78,1.78]

Favours ASA + MCP — Favours sumatriptan



Analysis 18.4. Comparison 18 Oral sumatriptan 100 mg versus acetylsalicylic acid 900 mg + metoclopramide 10 mg, Outcome 4 Any adverse event within 24 hours.

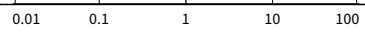


Comparison 19. Oral sumatriptan 200 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Headache relief at 2 h	3	749	Risk Ratio (M-H, Fixed, 95% CI)	2.84 [2.33, 3.46]
2 Any adverse event withdrawal	2	583	Risk Ratio (M-H, Fixed, 95% CI)	3.83 [1.46, 10.06]
3 Individual adverse events	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Nausea/vomiting	3	681	Risk Ratio (M-H, Fixed, 95% CI)	3.22 [1.90, 5.43]
3.2 Mouth disorder/disturbance of taste	2	605	Risk Ratio (M-H, Fixed, 95% CI)	3.01 [1.34, 6.78]
3.3 Chest pain/symptoms	2	605	Risk Ratio (M-H, Fixed, 95% CI)	4.41 [0.54, 36.34]
3.4 Paraesthesia/numbness	2	605	Risk Ratio (M-H, Fixed, 95% CI)	5.09 [0.92, 28.03]
3.5 Drowsiness/somnolence	2	605	Risk Ratio (M-H, Fixed, 95% CI)	6.18 [1.43, 26.68]

Analysis 19.1. Comparison 19 Oral sumatriptan 200 mg versus placebo, Outcome 1 Headache relief at 2 h.

Study or subgroup	Sumatriptan 200 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Banerjee 1992	21/34	12/37		12.35%	1.9[1.12,3.25]
Dahlof 1991	185/255	48/182		60.19%	2.75[2.13,3.55]
Patten 1991	105/140	22/101		27.46%	3.44[2.35,5.04]
Total (95% CI)	**429**	**320**		**100%**	**2.84[2.33,3.46]**
Total events: 311 (Sumatriptan 200 mg), 82 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=3.18, df=2(P=0.2); I^2=37.03%					
Test for overall effect: Z=10.35(P<0.0001)					



Favours placebo — Favours sumatriptan

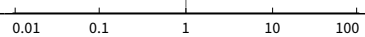
Analysis 19.2. Comparison 19 Oral sumatriptan 200 mg versus placebo, Outcome 2 Any adverse event withdrawal.

Study or subgroup	Sumatriptan 200 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Banerjee 1992	4/37	2/39		35.81%	2.11[0.41,10.83]
Dahlof 1991	20/295	3/212		64.19%	4.79[1.44,15.92]
Total (95% CI)	**332**	**251**		**100%**	**3.83[1.46,10.06]**
Total events: 24 (Sumatriptan 200 mg), 5 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.64, df=1(P=0.42); I^2=0%					
Test for overall effect: Z=2.73(P=0.01)					

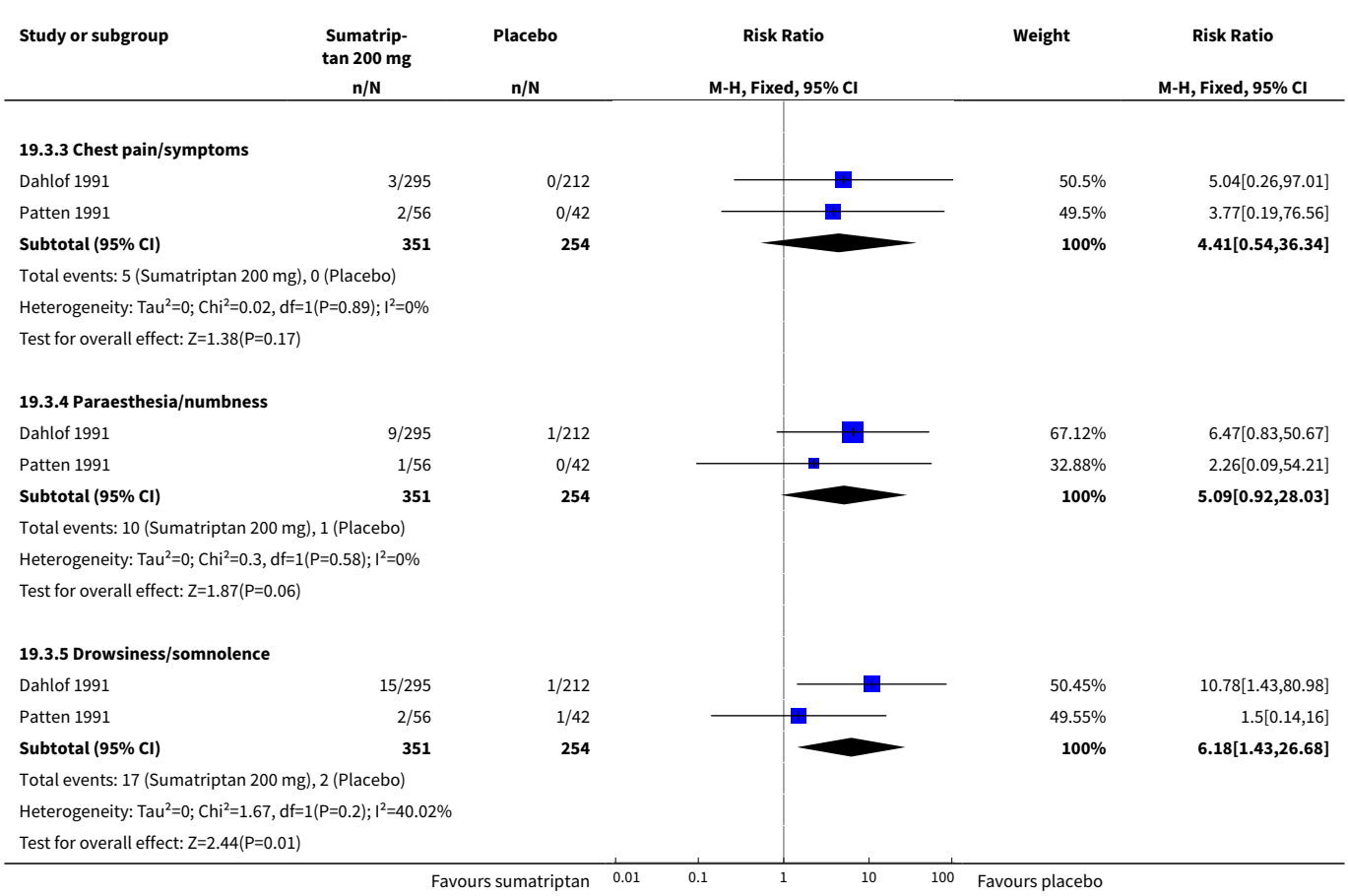
Favours placebo — Favours sumatriptan

Analysis 19.3. Comparison 19 Oral sumatriptan 200 mg versus placebo, Outcome 3 Individual adverse events.

Study or subgroup	Sumatriptan 200 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
19.3.1 Nausea/vomiting					
Banerjee 1992	9/37	3/39		16.22%	3.16[0.93,10.78]
Dahlof 1991	50/295	11/212		71.09%	3.27[1.74,6.12]
Patten 1991	8/56	2/42		12.69%	3[0.67,13.4]
Subtotal (95% CI)	**388**	**293**		**100%**	**3.22[1.9,5.43]**
Total events: 67 (Sumatriptan 200 mg), 16 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.01, df=2(P=0.99); I^2=0%					
Test for overall effect: Z=4.36(P<0.0001)					
19.3.2 Mouth disorder/disturbance of taste					
Dahlof 1991	24/295	4/212		57.59%	4.31[1.52,12.24]
Patten 1991	5/56	3/42		42.41%	1.25[0.32,4.94]
Subtotal (95% CI)	**351**	**254**		**100%**	**3.01[1.34,6.78]**
Total events: 29 (Sumatriptan 200 mg), 7 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.03, df=1(P=0.15); I^2=50.68%					
Test for overall effect: Z=2.67(P=0.01)					



Favours sumatriptan — Favours placebo

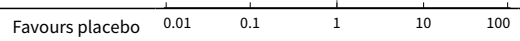


Comparison 20. Oral sumatriptan 300 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Headache relief at 2 h	2	709	Risk Ratio (M-H, Fixed, 95% CI)	2.72 [2.19, 3.36]
2 Individual adverse events	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Nausea/vomiting	2	624	Risk Ratio (M-H, Fixed, 95% CI)	2.90 [1.62, 5.20]
2.2 Mouth disorder/disturbance of taste	2	624	Risk Ratio (M-H, Fixed, 95% CI)	5.51 [2.56, 11.88]
2.3 Chest pain/symptoms	2	624	Risk Ratio (M-H, Fixed, 95% CI)	17.32 [2.36, 126.94]
2.4 Paraesthesia/numbness	2	624	Risk Ratio (M-H, Fixed, 95% CI)	9.86 [1.89, 51.37]
2.5 Drowsiness/somnolence	2	624	Risk Ratio (M-H, Fixed, 95% CI)	6.89 [1.62, 29.26]

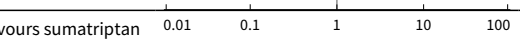
Analysis 20.1. Comparison 20 Oral sumatriptan 300 mg versus placebo, Outcome 1 Headache relief at 2 h.

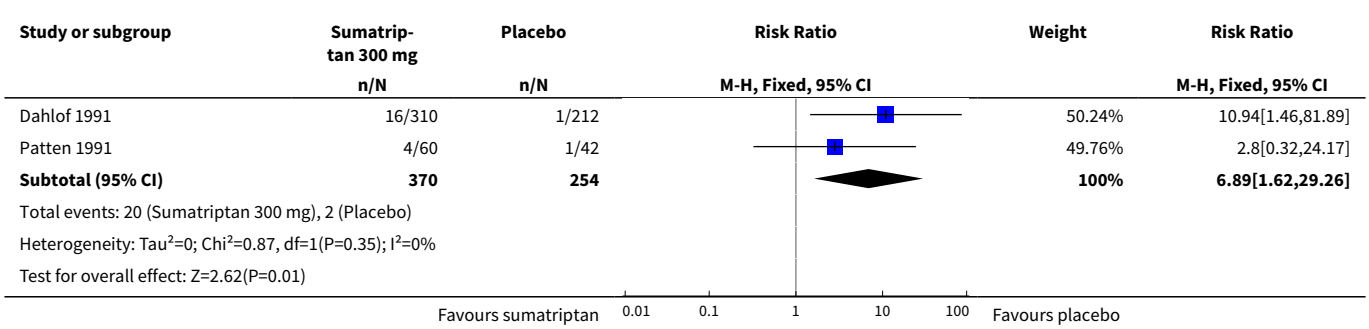
Study or subgroup	Sumatriptan 300 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Dahlof 1991	179/271	48/182		68.31%	2.5[1.94,3.24]
Patten 1991	107/155	22/101		31.69%	3.17[2.16,4.65]
Total (95% CI)	**426**	**283**		**100%**	**2.72[2.19,3.36]**
Total events: 286 (Sumatriptan 300 mg), 70 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1, df=1(P=0.32); I^2=0.05%					
Test for overall effect: Z=9.15(P<0.0001)					



Analysis 20.2. Comparison 20 Oral sumatriptan 300 mg versus placebo, Outcome 2 Individual adverse events.

Study or subgroup	Sumatriptan 300 mg n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
20.2.1 Nausea/vomiting					
Dahlof 1991	47/310	11/212		84.74%	2.92[1.55,5.5]
Patten 1991	8/60	2/42		15.26%	2.8[0.63,12.53]
Subtotal (95% CI)	**370**	**254**		**100%**	**2.9[1.62,5.2]**
Total events: 55 (Sumatriptan 300 mg), 13 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.96); I^2=0%					
Test for overall effect: Z=3.58(P=0)					
20.2.2 Mouth disorder/disturbance of taste					
Dahlof 1991	43/310	4/212		57.38%	7.35[2.68,20.18]
Patten 1991	13/60	3/42		42.62%	3.03[0.92,9.99]
Subtotal (95% CI)	**370**	**254**		**100%**	**5.51[2.56,11.88]**
Total events: 56 (Sumatriptan 300 mg), 7 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.28, df=1(P=0.26); I^2=21.7%					
Test for overall effect: Z=4.36(P<0.0001)					
20.2.3 Chest pain/symptoms					
Dahlof 1991	16/310	0/212		50.3%	22.6[1.36,374.69]
Patten 1991	8/60	0/42		49.7%	11.98[0.71,202.12]
Subtotal (95% CI)	**370**	**254**		**100%**	**17.32[2.36,126.94]**
Total events: 24 (Sumatriptan 300 mg), 0 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.1, df=1(P=0.75); I^2=0%					
Test for overall effect: Z=2.81(P=0.01)					
20.2.4 Paraesthesia/numbness					
Dahlof 1991	19/310	1/212		66.94%	12.99[1.75,96.33]
Patten 1991	2/60	0/42		33.06%	3.52[0.17,71.59]
Subtotal (95% CI)	**370**	**254**		**100%**	**9.86[1.89,51.37]**
Total events: 21 (Sumatriptan 300 mg), 1 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.52, df=1(P=0.47); I^2=0%					
Test for overall effect: Z=2.72(P=0.01)					
20.2.5 Drowsiness/somnolence					





APPENDICES

Appendix 1. Definitions

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

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

Appendix 2. Search strategy for MEDLINE (via OVID)

1. Serotonin Agonists/ OR Tryptamines/
2. (sumatriptan OR Imitrex OR Imigran).mp.
3. 1 OR 2
4. Headache/ OR exp Headache Disorders/ OR exp Migraine Disorders/
5. (headach* OR migrain* OR cephalgi* OR cephalalgi*).mp.
6. 4 OR 5
7. randomized controlled trial.pt.
8. controlled clinical trial.pt.
9. randomized.ab.
10. placebo.ab.

11.drug therapy.fs.
12.randomly.ab.
13.trial.ab.
14.groups.ab.
15.OR/7-14
16.3 AND 6 AND 15

Appendix 3. Search strategy for EMBASE (via OVID)

1. Serotonin Agonists/ OR Tryptamines/
2. (sumatriptan OR Imitrex OR Imigran).mp.
3. 1 OR 2
4. exp Headache and facial pain
5. exp Migraine
6. (headach* OR migrain* OR cephalgi* OR cephalalgi*).mp.
7. 4 OR 5 OR 6
8. clinical trials.sh.
9. controlled clinical trials.sh.
10. randomized controlled trial.sh.
11. double-blind procedure.sh.
12. (clin* adj25 trial*).ab.
13. ((doubl* or trebl* or tripl*) adj25 (blind* or mask*)).ab.
14. placebo*.ab.
15. random*.ab.
16. OR/8-15
17. 3 AND 7 AND 16

Appendix 4. Search strategy for CENTRAL

1. MeSH descriptor Serotonin Agonists OR MeSH descriptor Tryptamines
2. (sumatriptan OR Imitrex OR Imigran):ti,ab,kw
3. 1 OR 2
4. MeSH descriptor Headache/ OR MeSH descriptor Headache Disorders explode all trees
5. MeSH descriptor Migraine Disorders explode all trees
6. (headach* OR migrain* OR cephalgi* OR cephalalgi*):ti,ab,kw
7. 4 OR 5 OR 6
8. 3 AND 7
9. Limit 8 to Clinical Trials (CENTRAL)

Appendix 5. Summary of outcomes: efficacy

Study ID	Treatment	Headache relief 1 h	Headache relief 2 h	Pain-free 1 h	Pain-free 2 h	Sustained headache relief 24 h	Sustained pain-free 24 h	Use of rescue medication
160-104	Numbers of participants treating first attack: (1) Sumatriptan 25 mg, n = 180 (2) Sumatriptan 50 mg, n = 181 (3) Eletriptan 40 mg, n = 184 (4) Eletriptan 80 mg, n = 180 (5) Placebo, n = 93	1st attack: (1) 42/180 (2) 48/181 (3) 38/184 (4) 61/180 (5) 20/93	1st attack: (1) 90/180 (2) 98/181 (3) 109/184 (4) 119/180 (5) 34/93	No data	1st attack: (1) 29/180 (2) 31/181 (3) 34/184 (4) 45/180 (5) 8/93	No data	No data	No useable data
Banerjee 1992	(1) Sumatriptan (dispersible) 200 mg, n = 37 (34 for efficacy) (2) Placebo, n = 39 (37 for efficacy)	No data	1st attack: (1) 21/34 (2) 12/37	No data	1st attack: (1) 5/34 (2) 1/37	No data	No data	At 2 h: (1) 9/37 (2) 22/39
Brandes 2007	Study 1 (1) Sumatriptan 85 mg, n = 415 (365 for efficacy) (2) Naproxen 500 mg, n = 419 (361 for efficacy) (3) Sumatriptan 85 mg + naproxen 500 mg, n = 422 (370 for efficacy) (4) Placebo, n = 421 (365 for efficacy) Study 2 (1) Sumatriptan 85 mg, n = 434 (370 for efficacy) (2) Naproxen 500 mg, n = 434 (371 for efficacy) (3) Sumatriptan 85 mg + naproxen 500 mg, n = 433 (367 for efficacy)	No data	Study 1 (1) 200/365 (2) 157/361 (3) 237/370 (4) 102/365 Study 2 (1) 182/370 (2) 158/371 (3) 207/367 (4) 109/387	No data	Study 1 (1) 90/365 (2) 53/361 (3) 125/370 (4) 33/365 Study 2 (1) 82/370 (2) 57/371 (3) 107/367 (4) 37/387	Study 1 (1) 127/365 (2) 107/361 (3) 174/370 (4) 64/365 Study 2 (1) 121/370 (2) 102/371 (3) 158/367 (4) 64/387	Study 1 (1) 59/365 (2) 37/361 (3) 90/370 (4) 30/365 Study 2 (1) 51/370 (2) 37/371 (3) 83/367 (4) 25/387	At 24 h: Study 1 (1) 115/361 (2) 135/356 (3) 81/364 (4) 192/360 Study 2 (1) 137/362 (2) 143/364 (3) 83/362 (4) 223/382

(Continued)

	(4) Placebo, n = 435 (387 for efficacy)							
Bussone 2000	(1) Sumatriptan 50 mg, n = 156 (2) Placebo, n = 56	No data	(1) 87/156 (2) 14/56	No data	No data	No data	No data	No useable data
Carpay 2004	(1) Sumatriptan (fast disintegrating) 50 mg, n = 141 (2) Sumatriptan (fast disintegrating) 100 mg, n = 148 (3) Placebo, n = 155	No data	No data	(1) 50/141 (2) 63/148 (3) 29/155	(1) 70/141 (2) 94/148 (3) 30/155	No data	(1) 44/141 (2) 57/148 (3) 15/155	No data
Cutler 1995	(1) Sumatriptan 25 mg, n = 66 (2) Sumatriptan 50 mg, n = 62 (3) Sumatriptan 100 mg, n = 66 (4) Placebo, n = 65	No data	(1) 34/66 (2) 31/62 (3) 37/66 (4) 17/65	No data	(1) 14/66 (2) 10/62 (3) 15/66 (4) 5/65	No data	No data	No data
Dahlof 1991	(1) Sumatriptan 100 mg, n = 305 (275 with moderate or severe baseline pain intensity) (2) Sumatriptan 200 mg, n = 283 (255 with moderate or severe baseline pain intensity) (3) Sumatriptan 300 mg, n = 299 (271 with moderate or severe baseline pain intensity) (4) Placebo, n = 205 (182 with moderate or severe baseline pain intensity)	No data	(1) 180/275 (2) 185/255 (3) 179/271 (4) 48/182	No data	No data	No data	No data	No useable data
Dahlof 2009	(1) Sumatriptan 50 mg, n = 136 (2) Tonabersat 20 mg, n = 134 (3) Tonabersat 40 mg, n = 137 (4) Placebo, n = 134	(1) 41/136 (2) 28/134 (3) 24/137 (4) 29/134	(1) 70/136 (2) 39/134 (3) 43/137 (4) 36/134	(1) 8/136 (2) 2/134 (3) 4/137 (4) 1/134	(1) 32/136 (2) 7/134 (3) 6/137 (4) 8/134	No data	No data	At 3 h: (1) 29/136 (2) 40/134 (3) 41/137 (4) 39/134
Diener 2004a	(1) Sumatriptan 50 mg, n = 135 (2) Effervescent acetylsalicylic acid 1000 mg, n = 147 (146 for efficacy)	(1) 32/135 (2) 37/146	(1) 66/135 (2) 72/146	(1) 7/135 (2) 6/146	(1) 33/135 (2) 37/146	No data	No data	At 24 h: (1) 53/135

(Continued)

	(3) Placebo, n = 153 (152 for efficacy)	(3) 23/152	(3) 50/152	(3) 5/152	(3) 22/152			(2) 62/146 (3) 98/152
Diener 2004b	(1) Sumatriptan 50 mg, n = 226 (2) Ibuprofen 400 mg, n = 212 (3) Effervescent acetylsalicylic acid 1000 mg, n = 222 (4) Placebo, n = 222	(1) 54/224 (2) 65/211 (3) 76/221 (4) 25/222	(1) 125/224 (2) 127/211 (3) 116/221 (4) 68/222	(1) 12/224 (2) 21/211 (3) 14/221 (4) 7/222	(1) 83/224 (2) 70/211 (3) 60/221 (4) 28/222	No useable data	No data	At 2 h: (1) 92/224 (2) 87/211 (3) 99/221 (4) 147/222
DKSMSG 1999	(1) Sumatriptan 100 mg, n = 130 (2) Diclofenac-potassium 50 mg, n = 131 (3) Diclofenac-potassium 100 mg, n = 122 (4) Placebo, n = 131	No useable data	No useable data	No data	No useable data	No data	No data	At 24 h: (1) 47/115 (2) 41/115 (3) 41/115 (4) 69/115
Dodick 2002	Protocol CL13 (1) Sumatriptan 100 mg, n = 193 (2) Almotriptan 12.5 mg, n = 183 (3) Placebo, n = 99	No data	No data	No data	(1) 64/193 (2) 51/183 (3) 16/99	No data	(1) 54/193 (2) 46/183 (3) 12/99	At 24 h: (1) 66/193 (2) 70/183 (3) 52/99
Dowson 2002	(1) Sumatriptan 100 mg, n = 194 (2) Almotriptan 12.5 mg, n = 184 (3) Almotriptan 25 mg, n = 191 (4) Placebo, n = 99	(1) 73/194 (2) 65/184 (3) 59/191 (4) 29/99	(1) 123/194 (2) 104/184 (3) 108/191 (4) 42/99	(1) 15/194 (2) 9/184 (3) 21/191 (4) 5/99	(1) 65/194 (2) 51/184 (3) 66/191 (4) 15/99	No data	No data	At 2 h: (1) 63/194 (2) 71/184 (3) 73/191 (4) 55/99
Ensink 1991	(1) Sumatriptan 100 mg, n = 148 (131 with moderate or severe baseline pain intensity) (2) Placebo, n = 84 (78 with moderate or severe baseline pain intensity)	No data	(1) 60/131 (2) 14/78	No data	(1) 34/131 (2) 4/78	No data	No data	No useable data

(Continued)

Freitag 2001	(1) Sumatriptan 25 mg (+ additional dose of 25 mg at 2 h), n = 61 (2) Isometheptene combination 2 doses (+ additional single doses at 1, 2 and 3 h), n = 65	(1) 18/40 (2) 19/42	No data	No data	No data	No data	No data	No data
Gallagher 2000	(1) Sumatriptan 25 mg, n = 336 (306 for efficacy) (2) Sumatriptan 50 mg, n = 338 (306 for efficacy) (3) Zolmitriptan 2.5 mg, n = 327 (295 for efficacy) (4) Zolmitriptan 5 mg, n = 337 (305 for efficacy)	(1) 101/306 (2) 106/306 (3) 103/295 (4) 114/305	(1) 182/306 (2) 195/306 (3) 198/295 (4) 198/305	No data	No data	(1) 101/306 (2) 117/306 (3) 120/295 (4) 130/305	No data	No data
Geraud 2000	(1) Sumatriptan 100 mg, n = 504 (2) Zolmitriptan 5 mg, n = 498 (3) Placebo, n = 56	(1) 171/504 (2) 163/498 (3) 11/56	(1) 304/504 (2) 288/498 (3) 24/56	(1) 54/504 (2) 37/498 (3) 1/56	(1) 150/504 (2) 144/498 (3) 7/56	(1) 195/504 (2) 180/498 (3) 14/56	No data	At 24 h: (1) 192/504 (2) 189/498 (3) 32/56
GL/MIG/001/92	(1) Sumatriptan 100 mg, n = 305 (242 with moderate or severe baseline pain intensity) (2) Paracetamol 1000 mg + metoclopramide 10 mg, n = 302 (227 with moderate or severe baseline pain intensity)	No data	1st attack: (1) 118/242 (2) 103/227	No data	No data	No data	No data	1st attack, at 24 h: (1) 79/288 (2) 91/286
GL/MIG/001A/92	(1) Sumatriptan 100 mg, n = 348 (272 with moderate or severe baseline pain intensity) (2) Paracetamol 1000 mg + metoclopramide 10 mg, n = 373 (294 with moderate or severe baseline pain intensity)	No data	1st attack: (1) 115/272 (2) 122/294	No data	No data	No data	No data	1st attack, at 24 h: (1) 119/318 (2) 154/351
GL/MIG/002	(1) Sumatriptan 100 mg, n = 374 (262 with moderate or severe baseline pain intensity) (2) Migraleve (buclizine hydrochloride 12.5 mg + paracetamol 1000 mg + codeine phos-	No data	1st attack: (1) 131/262 (2) 111/275	No data	No data	No data	No data	1st attack, at 24 h: (1) 71/351 (2) 106/358

(Continued)

	phate 16 mg), n = 378 (275 with moderate or severe baseline pain intensity)							
GL/MIG/002A	(1) Sumatriptan 100 mg, n = 342 (261 with moderate or severe baseline pain intensity) (2) Migraleve (buclizine hydrochloride 12.5 mg + paracetamol 1000 mg + codeine phosphate 16 mg), n = 332 (257 with moderate or severe baseline pain intensity)	No data	No useable data	No data	No data	No data	No data	1st attack, at 24 h: (1) 60/305 (2) 106/308
GL/MIG/009	(1) Sumatriptan 100 mg, n = 255 (203 with moderate or severe baseline pain intensity) (2) Migril (ergotamine tartrate 2 mg + cyclizine hydrochloride 50 mg + caffeine hydrate 100 mg), n = 258 (204 with moderate or severe baseline pain intensity)	1st attack: (1) 69/203 (2) 56/204	1st attack: (1) 95/203 (2) 76/204	1st attack: (1) 24/203 (2) 11/204	1st attack: (1) 56/203 (2) 39/204	No data	No data	1st attack, at 24 h: (1) 27/234 (2) 27/234
Goadsby 1991	Number of attacks in efficacy population: (1) Sumatriptan 100 mg, n = 94 (89 of moderate or severe intensity) (2) Placebo, n = 94 (93 of moderate or severe intensity)	No data	(1) 45/89 (2) 9/93	No data	No data	No data	No data	At 2 h: (1) 39/94 (2) 83/94
Goadsby 2000	(1) Sumatriptan 100 mg, n = 129 (2) Eletriptan 20 mg, n = 144 (3) Eletriptan 40 mg, n = 136 (4) Eletriptan 80 mg, n = 141 (5) Placebo, n = 142	(1) 23/129 (2) 31/144 (3) 44/136 (4) 48/141 (5) 15/142	(1) 63/129 (2) 70/144 (3) 76/136 (4) 91/141 (5) 30/142	(1) 7/129 (2) 3/144 (3) 9/136 (4) 20/141 (5) 3/142	(1) 26/129 (2) 25/144 (3) 34/136 (4) 44/141 (5) 8/142	No data	No data	At 24 h: (1) 37/129 (2) 43/144 (3) 39/136 (4) 37/141 (5) 75/142
Goldstein 1998	(1) Sumatriptan 25 mg, n = 563 (2) Sumatriptan 50 mg, n = 566 (3) Rizatriptan 5 mg, n = 557 (4) Rizatriptan 10 mg, n = 567 (5) Placebo, n = 141	(1) 194/563 (2) 218/566 (3) 209/557 (4) 236/567 (5) no data	(1) 349/563 (2) 385/566 (3)	(1) 36/563 (2) 43/566 (3) 61/557 (4) 63/567 (5) no data	(1) 158/563 (2) 209/566 (3) 184/557 (4) 232/567 (5) 13/141	No data	No data	1st attack, at 4 h: (1) 141/563 (2) 108/566 (3) 128/557

(Continued)

			379/557 (4) 408/567 (5) 54/141					(4) 108/567 (5) 63/141
Goldstein 2005	(1) Sumatriptan 50 mg, n = 67 (2) Acetaminophen 1000 mg + aspirin 1000 mg + caffeine 260 mg combination, n = 69 (3) Placebo, n = 35	(1) 23/46 (2) 25/50 (3) 8/27	(1) 30/46 (2) 42/50 (3) 14/27	No data	No data	No data	No data	At 4 h: (1) 8/67 (2) 1/69 (3) 5/35
Gruffyd-Jones 2001	(1) Sumatriptan 50 mg, n = 555 (508 for efficacy) (2) Zolmitriptan 2.5 mg, n = 551 (500 for efficacy) (3) Zolmitriptan 5 mg, n = 560 (514 for efficacy)	1st attack: (1) 224/508 (2) 215/500 (3) 206/514	1st attack: (1) 361/508 (2) 325/500 (3) 339/514	1st attack: (1) 66/508 (2) 50/500 (3) 62/514	1st attack: (1) 183/508 (2) 160/500 (3) 185/514	No useable data	1st attack: (1) 137/508 (2) 125/500 (3) 123/514	All attacks, at 24 h: (1) 620/2693 (2) 631/2671 (3) 608/2744
Havanka 2000	(1) Sumatriptan 100 mg, n = 98 (2) Naratriptan 1 mg, n = 85 (3) Naratriptan 2.5 mg, n = 87 (4) Naratriptan 5 mg, n = 93 (5) Naratriptan 7.5 mg, n = 93 (6) Naratriptan 10 mg, n = 96 (95 with moderate or severe baseline pain intensity) (7) Placebo, n = 91	(1) 34/98 (2) 21/85 (3) 26/87 (4) 32/93 (5) 40/93 (6) 38/95 (7) 18/91	(1) 59/98 (2) 49/85 (3) 45/87 (4) 50/93 (5) 63/93 (6) 66/95 (7) 28/91	No data	No data	No useable data	No data	At 24 h: (1) 25/98 (2) 40/85 (3) 30/87 (4) 36/93 (5) 23/93 (6) 21/96 (7) 60/91
Ishkanian 2007	(1) Sumatriptan 50 mg, n = 108 (2) Placebo, n = 108 (107 for efficacy)	No data	(1) 75/108 (2) 46/107	No data	(1) 26/108 (2) 22/107	No data	No data	At 24 h: (1) 37/108 (2) 46/107

(Continued)

Jelinski 2006	(1) Sumatriptan 50 mg, n = 126 (2) Sumatriptan 100 mg, n = 126 (3) Placebo, n = 109	No data	No data	(1) 30/126 (2) 30/126 (3) 8/109	(1) 51/126 (2) 63/126 (3) 17/109	No data	(1) 30/126 (2) 34/126 (3) 7/109	No data
Kaniecki 2006	(1) Sumatriptan 100 mg, n = 131 (2) Placebo, n = 127	No data	(1) 64/131 (2) 47/127	No data	(1) 32/131 (2) 18/127	(1) 43/131 (2) 19/127	(1) 24/131 (2) 7/127	At 24 h: (1) 55/131 (2) 79/127
Kolodny 2004	(1) Sumatriptan 25 mg, n = 554 (290 1st attack only) (2) Sumatriptan 50 mg, n = 550 (285 1st attack only) (3) Rizatriptan 5 mg, n = 536 (288 1st attack only) (4) Rizatriptan 10 mg, n = 547 (296 1st attack only) (5) Placebo, n = 288	(1) 181/554 (2) 191/550 (3) 195/536 (4) 220/547 (5) no data	(1) 320/554 (2) 361/550 (3) 352/536 (4) 372/547 (5) no data	No data	(1) 152/554 (2) 185/550 (3) 179/536 (4) 208/547 (5) no data	No data	No data	1st attack, at 4 h: (1) 66/290 (2) 59/285 (3) 85/288 (4) 67/296 (5) 112/288
Kudrow 2005	(1) Sumatriptan 50 mg, n = 144 (2) Valdecoxib 20 mg, n = 137 (3) Valdecoxib 40 mg, n = 152 (4) Placebo, n = 141	No data	(1) 60/144 (2) 61/137 (3) 72/152 (4) 42/141	No data	No data	No data	No data	No useable data
Latere 1991	(1) Sumatriptan (dispersible) 100 mg, n = 288 (220 with moderate or severe baseline pain intensity) (2) Cafergot, n = 289 (246 with moderate or severe baseline pain intensity)	No data	1st attack: (1) 145/220 (2) 118/246	No data	1st attack: (1) 77/220 (2) 32/246	No data	No data	At 2 h: (1) 69/288 (2) 127/289
Lines 2001	(1) Sumatriptan 50 mg, n = 356 (2) Rizatriptan 5 mg, n = 349 (3) Placebo, n = 80	No data	(1) 239/356 (2) 220/349 (3) 18/80	No data	No data	No data	No data	No data

(Continued)

Lipton 2000	Treated attacks: (1) Sumatriptan 50 mg, n = 870 (2) Placebo, n = 240	No data	All attacks: (1) 409/870 (2) 82/240	No data	All attacks (1) 157/870 (2) 17/240	No data	No data	All attacks, at 24 h: (1) 61/870 (2) 20/240
Matthew 2003	(1) Sumatriptan 100 mg, n = 831 (2) Eletriptan 40 mg, n = 822 (3) Placebo, n = 419	(1) 214/831 (2) 272/822 (3) 44/419	(1) 471/831 (2) 522/822 (3) 105/419	(1) 40/831 (2) 56/822 (3) 0/419	(1) 216/831 (2) 280/822 (3) 20/419	(1) 276/831 (2) 342/822 (3) 58/419	No data	At 24 h: (1) 224/831 (2) 164/822 (3) 222/419
Myllyla 1998	(1) Sumatriptan 100 mg (+ optional dose of placebo after 1 h), n = 46 (42 for efficacy) (2) Tolfenamic acid 200 mg (+ optional 2nd dose after 1 h), n = 47 (43 for efficacy) (3) Placebo (+ optional dose of placebo after 1 h), n = 46 (41 for efficacy)	No data	1st attack: (1) 33/42 (2) no useable data (3) 12/41	No data	1st attack: (1) 21/42 (2) no useable data (3) 3/41	No data	No data	No useable data
Nappi 1994	(1) Sumatriptan 100 mg, n = 158 (148 with moderate or severe baseline pain intensity) (2) Placebo, n = 86 (81 with moderate or severe baseline pain intensity)	No data	(1) 73/142 (2) 25/81	No data	(1) 34/142 (2) 8/81	No data	No data	No useable data
Nett 2003	(1) Sumatriptan 50 mg, n = 124 (124 for efficacy, 116 for per-protocol efficacy) (2) Sumatriptan 100 mg, n = 122 (122 for efficacy, 115 for per-protocol efficacy) (3) Placebo, n = 123 (122 for efficacy, 118 for per-protocol efficacy)	No data	No data	(1) 30/124 (2) 37/122 (3) 18/122	(1) 62/124 (2) 74/122 (3) 35/122	No data	(1) 35/116 (2) 36/115 (3) 17/118	No data
Patten 1991	(1) Sumatriptan (dispersible) 100 mg, n = 142 (2) Sumatriptan (dispersible) 200 mg, n = 140 (3) Sumatriptan (dispersible) 300 mg, n = 155	No data	1st attack: (1) 95/142 (2) 105/140 (3) 107/155 (4) 22/101	No data	No data	No data	No data	No data

(Continued)

	(4) Placebo, n = 101							
Pfaffenrath 1998	(1) Sumatriptan 25 mg, n = 303 (286 with moderate or severe baseline pain intensity) (2) Sumatriptan 50 mg, n = 303 (285 with moderate or severe baseline pain intensity) (3) Sumatriptan 100 mg, n = 298 (277 with moderate or severe baseline pain intensity) (4) Placebo, n = 99 (91 with moderate or severe baseline pain intensity)	1st attack: (1) 83/286 (2) 123/285 (3) 100/277 (4) 13/91	1st attack: (1) 140/286 (2) 180/285 (3) 175/277 (4) 27/91	No data	No useable data	No data	No data	No data
Pini 1999	(1) Sumatriptan 50 mg, n = 137 (106 for efficacy) (2) Placebo, n = 82 (61 for efficacy)	No data	No data	No data	(1) 36/106 (2) 9/61	No data	No data	At 4 h: (1) 22/95 (2) 26/54
Pini 1995	(1) Sumatriptan 100 mg, n = 151 (2) Placebo, n = 87	No data	No data	No data	No data	No data	No data	No useable data
Sandrini 2002	(1) Sumatriptan 50 mg, n = 181 (2) Sumatriptan 100 mg, n = 170 (3) Eletriptan 40 mg, n = 175 (4) Eletriptan 80 mg, n = 164 (5) Placebo, n = 84	(1) 42/181 (2) 45/170 (3) 52/175 (4) 58/164 (5) 10/84	(1) 88/181 (2) 85/170 (3) 108/175 (4) 107/164 (5) 25/84	(1) 9/181 (2) 12/170 (3) 10/175 (4) 20/164 (5) 1/84	(1) 33/181 (2) 29/170 (3) 52/175 (4) 59/164 (5) 3/84	(1) 61/181 (2) 64/170 (3) 88/175 (4) 87/164 (5) 18/84	(1) 20/181 (2) 24/170 (3) 42/175 (4) 46/164 (5) 3/84	No useable data
Sandrini 2007	(1) Sumatriptan 50 mg, n = 139 (138 for efficacy) (2) Indoprocaf, n = 143	No data	1st attack: (1) 79/138 (2) 82/143	All attacks: (1) 18/264 (2) 14/276	1st attack: (1) 49/138 (2) 45/143	1st attack: (1) 60/138 (2) 64/143	1st attack: (1) 29/138 (2) 23/143	No useable data
Sargent 1995	(1) Sumatriptan 25 mg, n = 48 (2) Sumatriptan 50 mg, n = 46 (3) Sumatriptan 100 mg, n = 46 (4) Placebo, n = 47	(1) 12/48 (2) 6/46 (3) 10/46 (4) 3/47	(1) 25/48 (2) 25/46 (3) 26/46 (4) 8/47	No data	No data	No data	No data	No data

(Continued)

Savani 1999	(1) Sumatriptan 50 mg, n = 331 (2) Placebo, n = 154	1st attack: (1) 74/331 (2) 26/154	1st attack: (1) 140/331 (2) 32/154	No data	1st attack: (1) 63/331 (2) 5/154	No useable data	No data	No useable data
Schulman 2003	(1) Sumatriptan 50 mg, n = 16 (2) Sumatriptan 50 mg + metoclopramide 10 mg, n = 16	No data	(1) 5/16 (2) 7/16	No data	No data	No data	No data	No data
Sheftell 2005	Study 1: (1) Sumatriptan (rapid-release) 50 mg, n = 494 (448 for efficacy) (2) Sumatriptan (rapid-release) 100 mg, n = 488 (462 for efficacy) (3) Placebo, n = 495 (456 for efficacy) Study 2: (1) Sumatriptan (rapid-release) 50 mg, n = 496 (454 for efficacy) (2) Sumatriptan (rapid-release) 100 mg, n = 485 (440 for efficacy) (3) Placebo, n = 494 (436 for efficacy)	No data	Study 1 (1) 310/448 (2) 331/462 (3) 208/456 Study 2 (1) 293/454 (2) 318/440 (3) 167/436	No data	Study 1 (1) 180/448 (2) 219/462 (3) 84/456 Study 2 (1) 178/454 (2) 207/440 (3) 53/436	Study 1 (1) 154/448 (2) 163/462 (3) 92/456 Study 2 (1) 173/454 (2) 181/440 (3) 69/436	Study 1 (1) 85/448 (2) 107/462 (3) 46/456 Study 2 (1) 96/454 (2) 108/440 (3) 21/436	No useable data
Smith 2005	(1) Sumatriptan 50 mg, n = 229 (226 for efficacy) (2) Sumatriptan 50 mg, + naproxen 500 mg, n = 251 (250 for efficacy) (3) Naproxen 500 mg, n = 250 (248 for efficacy) (4) Placebo, n = 241	(1) 52/226 (2) 73/250 (3) 67/248 (4) 29/241	(1) 111/226 (2) 163/250 (3) 114/248 (4) 65/241	(1) 9/226 (2) 20/250 (3) 7/248 (4) 2/241	(1) 45/226 (2) 85/250 (3) 45/248 (4) 14/241	(1) 66/226 (2) 115/250 (3) 62/248 (4) 41/241	(1) 25/226 (2) 63/250 (3) 30/248 (4) 12/241	At 24 h: (1) 115/226 (2) 88/250 (3) 129/248 (4) 154/241
Spierings 2001	(1) Sumatriptan 50 mg, n = 582 (2) Almotriptan 12.5 mg, n = 591	(1) 206/582 (2) 202/591	(1) 333/582 (2) 343/591	(1) 41/582 (2) 32/591	(1) 143/582 (2) 106/591	No data	No data	At 24 h: (1) 193/582 (2) 217/591

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Tfelt-Hansen 1995	(1) Sumatriptan 100 mg, n = 122 (2) Lysine acetylsalicylate 1620 mg + metoclopramide 10 mg, n = 137 (3) Placebo, n = 126	No data	1st attack: (1) 63/122 (2) 76/137 (3) 30/126	No data	1st attack: (1) 36/122 (2) 29/137 (3) 10/126	No data	No data	1st attack, at 24 h: (1) 77/122 (2) 74/137 (3) 102/126
Tfelt-Hansen 1998	(1) Sumatriptan 100 mg, n = 388 (2) Rizatriptan 5 mg, n = 164 (3) Rizatriptan 10 mg, n = 387 (4) Placebo, n = 160	(1) 108/388 (2) 49/164 (3) 141/387 (4) 32/160	(1) 239/388 (2) 99/164 (3) 258/387 (4) 64/160	(1) 30/388 (2) 11/164 (3) 40/387 (4) 5/160	(1) 127/388 (2) 41/164 (3) 155/387 (4) 15/160	No data	No data	At 2 h: (1) 77/387 (2) no data (3) 69/385 (4) 51/159
Tfelt-Hansen 2006	(1) Sumatriptan 50 mg, n = 53 (2) Placebo, n = 48	No data	No data	No data	(1) 20/53 (2) 8/48	No data	(1) 15/53 (2) 5/48	No data
Thomson 1992	(1) Sumatriptan 100 mg, n = 175 (153 with moderate or severe baseline pain intensity) (2) Aspirin 900 mg + metoclopramide 10 mg, n = 183 (163 with moderate or severe baseline pain intensity)	No data	1st attack: (1) 74/153 (2) 62/163	No data	1st attack: (1) 35/153 (2) 19/163	No data	No data	1st attack, at 48 h: (1) 57/168 (2) 101/181
Visser 1996	(1) Sumatriptan 100 mg, n = 72 (2) Rizatriptan 10 mg, n = 89 (3) Rizatriptan 20 mg, n = 82 (4) Rizatriptan 40 mg, n = 121 (5) Placebo, n = 85	(1) 17/72 (2) 22/89 (3) 24/82 (4) 47/121 (5) 12/85	(1) 33/72 (2) 46/89 (3) 46/82 (4) 80/121 (5) 15/85	No data	(1) 16/72 (2) 23/89 (3) 29/82 (4) 59/121 (5) 3/85	No data	No data	No data
Winner 2003	Study 1: (1) Sumatriptan 50 mg, n = 122 (2) Sumatriptan 100 mg, n = 115 (3) Placebo, n = 117	No data	No data	Study 1 (1) 27/122 (2) 29/115 (3) 15/117	Study 1 (1) 59/122 (2) 61/115 (3) 34/117	No data	No data	No useable data

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Study 2:	Study 2	Study 2
(1) Sumatriptan 50 mg, n = 111	(1) 24/111	(1) 59/111
(2) Sumatriptan 100 mg, n = 107	(2) 30/107	(2) 66/107
(3) Placebo, n = 119	(3) 17/119	(3) 35/119

Appendix 6. Associated symptoms: presence two hours after treatment

Associated symptoms: symptom present 2 hours after taking study medication						
Intervention	**Studies**	**Attacks treated**	**Treatment (%)**	**Placebo (%)**	**Relative risk (95% CI)**	**NNTp (95% CI)**
Nausea						
Sumatriptan 25 mg versus placebo	5	1587	30	42	0.76 (0.66 to 0.88)	8.9 (6.0 to 17)
Sumatriptan 50 mg versus placebo (moderate or severe baseline pain intensity)	10	3098	31	42	0.79 (0.72 to 0.87)	9.3 (7.0 to 14)
Sumatriptan 50 mg versus placebo (mild baseline pain intensity)	5	1223	21	33	0.63 (0.52 to 0.76)	8.3 (5.9 to 14)
Sumatriptan 100 mg versus placebo (moderate or severe baseline pain intensity)	15	4927	35	46	0.77 (0.71 to 0.81)	9.0 (7.2 to 12)
Sumatriptan 100 mg versus placebo (mild baseline pain intensity)	5	1218	21	33	0.63 (0.52 to 0.76)	8.2 (5.8 to 14)
Sumatriptan 25 mg versus rizatriptan 5 mg	2	2210	29	22	1.3 (1.1 to 1.5)	-15 (-9.6 to -32)
Sumatriptan 25 mg versus rizatriptan 10 mg	2	2231	29	23	1.3 (1.1 to 1.5)	-17 (-10 to -44)
Sumatriptan 50 mg versus rizatriptan 5 mg	2	2209	28	22	1.2 (1.1 to 1.4)	-19 (-11 to -63)
Sumatriptan 50 mg versus rizatriptan 10 mg	2	2230	28	23	1.2 (1.0 to 1.4)	Not calculated
Sumatriptan 50 mg versus eletriptan 40 mg	2	686	34	27	1.2 (0.98 to 1.5)	Not calculated
Sumatriptan 50 mg versus eletriptan 80 mg	2	675	34	31	1.1 (0.88 to 1.4)	Not calculated
Sumatriptan 100 mg versus eletriptan 40 mg	3	2132	34	27	1.3 (1.1 to 1.5)	-13 (-8.8 to -28)
Sumatriptan 100 mg versus eletriptan 80 mg	2	548	38	29	1.3 (1.0 to 1.7)	-11 (-5.9 to -80)
Sumatriptan 100 mg versus ASA 900 mg + MCP 10 mg	2	612	45	45	1.0 (0.85 to 1.2)	Not calculated
Vomiting						
Sumatriptan 50 mg versus placebo	3	1438	4	4	1.0 (0.59 to 1.7)	Not calculated

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Sumatriptan 100 mg versus placebo	6	1335	9	10	0.93 (0.67 to 1.3)	Not calculated
Sumatriptan 25 mg versus rizatriptan 5 mg	2	2210	3	2	1.6 (0.90 to 2.8)	Not calculated
Sumatriptan 25 mg versus rizatriptan 10 mg	2	2231	3	2	1.4 (0.82 to 2.4)	Not calculated
Sumatriptan 50 mg versus rizatriptan 5 mg	2	2209	3	2	2.0 (1.1 to 3.4)	-60 (-34 to -290)
Sumatriptan 50 mg versus rizatriptan 10 mg	2	2230	3	2	1.7 (1.0 to 2.9)	Not calculated
Photophobia						
Sumatriptan 25 mg versus placebo	4	1185	50	67	0.77 (0.69 to 0.85)	5.7 (4.3 to 8.7)
Sumatriptan 50 mg versus placebo (moderate or severe baseline pain intensity)	9	2928	45	59	0.76 (0.71 to 0.82)	7.1 (5.6 to 9.5)
Sumatriptan 50 mg versus placebo (mild baseline pain intensity)	4	988	35	52	0.66 (0.57 to 0.77)	5.7 (4.2 to 8.7)
Sumatriptan 100 mg versus placebo (moderate or severe baseline pain intensity)	9	3381	38	55	0.71 (0.66 to 0.77)	5.8 (4.8 to 7.3)
Sumatriptan 100 mg versus placebo (mild baseline pain intensity)	4	983	28	52	0.54 (0.46 to 0.64)	4.2 (3.3 to 5.5)
Sumatriptan 25 mg versus rizatriptan 5 mg	2	2210	51	46	1.1 (1.0 to 1.2)	Not calculated
Sumatriptan 25 mg versus rizatriptan 10 mg	2	2231	51	42	1.2 (1.1 to 1.3)	-11 (-7.7 to -21)
Sumatriptan 50 mg versus effervescent ASA 1000 mg	2	727	27	30	0.90 (0.72 to 1.1)	Not calculated
Sumatriptan 50 mg versus rizatriptan 5 mg	2	2209	45	46	0.98 (0.89 to 1.1)	Not calculated
Sumatriptan 50 mg versus rizatriptan 10 mg	2	2230	45	42	1.1 (0.96 to 1.2)	Not calculated
Sumatriptan 50 mg versus eletriptan 40 mg	2	687	44	40	1.1 (0.93 to 1.3)	Not calculated
Sumatriptan 50 mg versus eletriptan 80 mg	2	678	44	32	1.4 (1.1 to 1.7)	-8.0 (-5.1 to -19)
Sumatriptan 100 mg versus eletriptan 40 mg	3	2134	39	32	1.2 (1.1 to 1.4)	-14 (-8.8 to -30)

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Sumatriptan 100 mg versus eletriptan 80 mg	2	551	45	30	1.5 (1.2 to 1.9)	-6.7 (-4.4 to -15)
Phonophobia						
Sumatriptan 25 mg versus placebo	2	958	40	47	0.83 (0.70 to 0.98)	15 (7.2 to 120)
Sumatriptan 50 mg versus placebo (moderate or severe baseline pain intensity)	7	2709	38	50	0.75 (0.69 to 0.82)	8.3 (6.3 to 12)
Sumatriptan 50 mg versus placebo (mild baseline pain intensity)	4	989	30	45	0.66 (0.56 to 0.78)	6.6 (4.7 to 11)
Sumatriptan 100 mg versus placebo (moderate or severe baseline pain intensity)	7	3158	34	48	0.70 (0.64 to 0.77)	7.3 (5.8 to 10)
Sumatriptan 100 mg versus placebo (mild baseline pain intensity)	4	981	20	45	0.45 (0.37 to 0.55)	4.1 (3.3 to 5.4)
Sumatriptan 25 mg versus rizatriptan 5 mg	2	2210	42	37	1.2 (1.0 to 1.3)	Not calculated
Sumatriptan 25 mg versus rizatriptan 10 mg	2	2231	42	34	1.2 (1.1 to 1.4)	-12 (-8.3 to -25)
Sumatriptan 50 mg versus effervescent ASA 1000 mg	2	727	26	27	0.96 (0.76 to 1.2)	Not calculated
Sumatriptan 50 mg versus rizatriptan 5 mg	2	2209	37	37	0.99 (0.89 to 1.1)	Not calculated
Sumatriptan 50 mg versus rizatriptan 10 mg	2	2230	37	34	1.1 (0.96 to 1.2)	Not calculated
Sumatriptan 50 mg versus eletriptan 40 mg	2	689	39	36	1.1 (0.91 to 1.3)	Not calculated
Sumatriptan 50 mg versus eletriptan 80 mg	2	679	39	32	1.2 (0.99 to 1.5)	-14 (-6.9 to 1900)
Sumatriptan 100 mg versus eletriptan 40 mg	2	1898	35	28	1.3 (1.1 to 1.5)	-14 (-8.7 to -32)
Functional disability						
Sumatriptan 25 mg versus placebo	3	486	42	58	0.75 (0.62 to 0.91)	6.4 (4.1 to 15)
Sumatriptan 50 mg versus placebo	4	747	44	59	0.76 (0.66 to 0.88)	6.7 (4.5 to 13)
Sumatriptan 100 mg versus placebo	6	1897	41	67	0.61 (0.56 to 0.67)	3.8 (3.3 to 4.6)

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Sumatriptan 50 mg versus eletriptan 40 mg	2	705	44	35	1.3 (1.1 to 1.5)	-11 (-6.0 to -46)
Sumatriptan 50 mg versus eletriptan 80 mg	2	690	44	33	1.3 (1.1 to 1.6)	-9.5 (-5.6 to -30)
Sumatriptan 100 mg versus eletriptan 40 mg	3	2231	35	27	1.3 (1.2 to 1.5)	-13 (-8.5 to -24)
Sumatriptan 100 mg versus eletriptan 80 mg	2	563	48	32	1.5 (1.2 to 1.8)	-6.6 (-4.3 to -14)

Appendix 7. Summary of outcomes: adverse events and withdrawals

Study ID	Treatment	> 1 dose of study medication available	Any AE	Specific AEs	Serious AEs	AE withdrawal	Other withdrawals/exclusions
160-104	Numbers of participants treating first attack: (1) Sumatriptan 25 mg, n = 180 (2) Sumatriptan 50 mg, n = 181 (3) Eletriptan 40 mg, n = 184 (4) Eletriptan 80 mg, n = 180 (5) Placebo, n = 93	Yes	Within 7 days: Attack 1 1st dose only: (1) 32/99 (2) 39/113 (3) 54/124 (4) 76/138 (5) 17/42	Occurring in > 5% of subjects in any treatment arm Attack 1 1st dose only: Asthenia: (1) 1/99; (2) 0/113; (3) 5/124; (4) 7/138; (5) 0/42 Dry mouth: (1) 3/99; (2) 2/113; (3) 4/124; (4) 9/138; (5) 2/42 Nausea: (1) 5/99; (2) 10/113; (3) 9/124; (4) 14/138; (5) 3/42 Dizziness: (1) 4/99; (2) 9/113; (3) 11/124; (4) 7/138; (5) 1/42 Paraesthesia: (1) 2/99; (2) 1/113; (3) 6/124; (4) 7/138; (5) 1/42 Somnolence: (1) 4/99; (2) 3/113; (3) 4/124; (4) 16/138; (5) 1/42	(1) 1/180 (ovarian cyst) (2) 0/181 (3) 1/184 (acute cerebral infarction - not related) (4) 1/180 (uterine haemorrhage) (5) 2/93 (urinary tract infection and ectopic pregnancy)	Attack 1: (1) 2/180 (2) 5/181 (3) 3/90 (4) 5/88 (5) 3/93	Other withdrawals (no further details): Attack 1 (1) 55/180 (2) 54/181 (3) 21/90 (4) 10/88 (5) 22/93
Banerjee 1992	(1) Sumatriptan (dispersible) 200 mg, n = 37 (2) Placebo, n = 39	No	Within 24 hours: (1) 13/37 (2) 6/39	Nausea/vomiting: (1) 9/37; (2) 3/39	(1) 0/37 (2) 1/39	(1) 4/37 (2) 2/39	No data
Brandes 2007	Study 1 (1) Sumatriptan 85 mg, n = 415 (365 for efficacy) (2) Naproxen 500 mg, n = 419 (361 for efficacy)	No	Within 24 hours: Study 1 (1) 89/365 (2) 48/361	Reported in 2% or more of participants in any treatment arm: Study 1 Dizziness: (1) 8/365; (2) 6/361; (3) 17/370; (4) 9/365	Study 1 (1) 1/365 (2) 0/361 (3) 0/370 (4) 0/365	No data	No data

(Continued)

	(3) Sumatriptan 85 mg + naproxen 500 mg, n = 422 (370 for efficacy) (4) Placebo, n = 421 (365 for efficacy) Study 2 (1) Sumatriptan 85 mg, n = 434 (370 for efficacy) (2) Naproxen 500 mg, n = 434 (371 for efficacy) (3) Sumatriptan 85 mg + naproxen 500 mg, n = 433 (367 for efficacy) (4) Placebo, n = 435 (387 for efficacy)		(3) 100/370 (4) 45/365 Study 2 (1) 105/370 (2) 52/371 (3) 97/367 (4) 39/387	Paraesthesia: (1) 9/365; (2) 2/361; (3) 11/370; (4) 1/365 Somnolence: (1) 7/365; (2) 6/361; (3) 11/370; (4) 8/365 Nausea: (1) 9/365; (2) 3/361; (3) 11/370; (4) 6/365 Dry mouth: (1) 5/365; (2) 1/361; (3) 8/370; (4) 3/365 Chest discomfort: (1) 5/365; (2) 1/361; (3) 8/370; (4) 0/365 Study 2 Somnolence: (1) 10/370; (2) 6/371; (3) 13/367; (4) 7/387 Dizziness: (1) 8/370; (2) 5/371; (3) 11/367; (4) 7/387 Paraesthesia: (1) 8/370; (2) 0/371; (3) 7/367; (4) 2/387 Nausea: (1) 12/370; (2) 2/371; (3) 13/367; (4) 4/387 Dyspepsia: (1) 11/370; (2) 4/371; (3) 9/367; (4) 2/387 Dry mouth: (1) 10/370; (2) 0/371; (3) 7/367; (4) 5/387	Study 2 (1) 0/370 (2) 0/371 (3) 0/367 (4) 0/387		
Bussone 2000	(1) Sumatriptan 50 mg, n = 156 (2) Placebo, n = 56	Yes	No useable data	No useable data - adverse events reported by body system rather than individually	(1) 0/156 (2) 0/56	5 (groups not reported)	60 other withdrawals: 33 failed to return, 18 lack

(Continued)

							of efficacy, 3 investigator's decision, 6 other reasons
Carpay 2004	(1) Sumatriptan (fast disintegrating) 50 mg, n = 141 (2) Sumatriptan (fast disintegrating) 100 mg, n = 148 (3) Placebo, n = 155	Yes	Within 24 hours: Drug-related (1) 14/137 (2) 24/142 (3) 8/153	Reported in ≥ 3% of participants in any treatment group: Nausea and vomiting: (1) 1/137; (2) 7/142; (3) 3/153 Chest symptoms: (1) 3/137; (2) 4/142; (3) 0/153 Malaise and fatigue: (1) 2/137; (2) 4/142; (3) 1/153	(1) 0/137 (2) 0/142 (3) 0/153	(1) 1/137 (2) 0/142 (3) 0/153	36 other withdrawals: 1 consent withdrawn, 9 lost to follow-up, 24 no occasion to treat migraine, 1 other and 1 missing data
Cutler 1995	(1) Sumatriptan 25 mg, n = 66 (2) Sumatriptan 50 mg, n = 62 (3) Sumatriptan 100 mg, n = 66 (4) Placebo, n = 65	No	Within 24 hours: (1) 47/66 (2) 42/62 (3) 42/66 (4) 48/65	Experienced by ≥ 3 participants in any treatment group: Nausea/vomiting: (1) 23/66; (2) 5/62; (3) 15/66; (4) 25/65 Migraine: (1) 17/66; (2) 23/62; (3) 20/66; (4) 26/65 Headache: (1) 15/66; (2) 18/62; (3) 17/66; (4) 20/65 Mouth disorder: (1) 6/66; (2) 11/62; (3) 5/66; (4) 12/65 Dizziness/vertigo: (1) 6/66; (2) 10/62; (3) 3/66; (4) 9/65 Drowsiness/sedation: (1) 6/66; (2) 5/62; (3) 5/66; (4) 9/65 Tingling: (1) 6/66; (2) 2/62; (3) 5/66; (4) 5/65	No data	1 (group not reported)	No data

(Continued)

				Sleep disturbance: (1) 0/66; (2) 2/62; (3) 2/66; (4) 5/65 Taste disturbance: (1) 5/66; (2) 2/62; (3) 6/66; (4) 5/65 Neck pain/stiffness: (1) 2/66; (2) 2/62; (3) 2/66; (4) 5/65			
Dahlof 1991	(1) Sumatriptan 100 mg, n = 305 (2) Sumatriptan 200 mg, n = 283 (3) Sumatriptan 300 mg, n = 299 (4) Placebo, n = 205	No	Within 24 hours: Drug-related (1) 113/313 (2) 139/295 (3) 164/310 (4) 36/212	Bad taste: (1) 16/313; (2) 24/295; (3) 43/310; (4) 4/212 Malaise/fatigue: (1) 19/313; (2) 27/295; (3) 31/310; (4) 4/212 Dizziness/vertigo: (1) 19/313; (2) 15/295; (3) 19/310; (4) 2/212 Drowsiness/sedation: (1) 6/313; (2) 15/295; (3) 16/310; (4) 1/212 Nausea and/or vomiting: (1) 34/313; (2) 50/295; (3) 47/310; (4) 11/212 Chest symptoms: (1) 6/313; (2) 3/295; (3) 16/310; (4) 0/212 Numbness/paraesthesia/ tingling: (1) 13/313; (2) 9/295; (3) 19/310; (4) 1/212 Feeling of heaviness: (1) 6/313; (2) 15/295; (3) 9/310; (4) 1/212 Weakness: (1) 13/313; (2) 12/295; (3) 6/310; (4) 1/212	(1) 2/313 (2) 1/295 (3) 1/310 (4) 0/212	(1) 10/313 (2) 20/295 (3) 26/310 (4) 3/212	38 excluded from efficacy analysis due to protocol violations
Dahlof 2009	(1) Sumatriptan 50 mg, n = 136	No	Within 6 days:	Occurring in ≥ 3% of participants:	2 (groups not reported)	(1) 0/136	147 other exclusions:

(Continued)

	(2) Tonabersat 20 mg, n = 134 (3) Tonabersat 40 mg, n = 137 (4) Placebo, n = 134		(1) 44/136 (2) 43/134 (3) 56/137 (4) 34/134	Dizziness: (1) 3/136; (2) 8/134; (3) 13/137; (4) 2/134 Paraesthesia: (1) 4/136; (2) 0/134; (3) 5/137; (4) 2/134 Vertigo: (1) 1/136; (2) 4/134; (3) 7/137; (4) 1/134 Nausea: (1) 4/136; (2) 6/134; (3) 11/137; (4) 3/134 Somnolence: (1) 3/136; (2) 2/134; (3) 5/137; (4) 1/134		(2) 0/134 (3) 0/137 (4) 0/134	88 did not have an attack meeting IHS criteria, 33 for protocol violations, 25 for vomiting within 1 h of treatment, 1 for treating a mild headache
Diener 2004a	(1) Sumatriptan 50 mg, n = 135 (2) Effervescent acetylsalicylic acid 1000 mg, n = 147 (146 for efficacy) (3) Placebo, n = 153 (152 for efficacy)	No	Within 24 hours: (1) 19/135 (2) 19/147 (3) 16/153	No useable data - only adverse events for single body system reported	No data	No data	2 excluded from efficacy analysis due to failure to return patient diaries
Diener 2004b	(1) Sumatriptan 50 mg, n = 226 (2) Ibuprofen 400 mg, n = 212 (3) Effervescent acetylsalicylic acid 1000 mg, n = 222 (4) Placebo, n = 222	No	Within 24 hours: (1) 45/226 (2) 26/212 (3) 36/222 (4) 32/222	No data	(1) 0/226 (2) 1/212 (3) 1/222 (4) 0/222	(1) 0/226 (2) 1/212 (3) 1/222 (4) 0/222	1 excluded from efficacy analysis due to failure to return patient diary
DKSMSG 1999	(1) Sumatriptan 100 mg, n = 130 (2) Diclofenac-potassium 50 mg, n = 131	No	Within 24 hours: (1) 43/130 (2) 25/131	Occurring in ≥ 2% participants for at least 1 treatment: Asthenia: (1) 4/130; (2) 1/131; (3) 1/122; (4) 2/131	(1) 0/130 (2) 0/131 (3) 0/122	(1) 0/130 (2) 0/131 (3) 2/122	25 other withdrawals: 5 withdrew consent, 1 no longer re-

(Continued)

	(3) Diclofenac-potassium 100 mg, n = 122 (4) Placebo, n = 131		(3) 18/122 (4) 26/131	Fatigue: (1) 7/130; (2) 5/131; (3) 1/122; (4) 4/131 Chest pain: (1) 4/130; (2) 0/131; (3) 0/122; (4) 1/131 Dizziness: (1) 7/130; (2) 1/131; (3) 0/122; (4) 3/131 Paraesthesia: (1) 5/130; (2) 2/131; (3) 0/122; (4) 1/131 Somnolence: (1) 3/130; (2) 8/131; (3) 1/122; (4) 3/131 Dyspepsia: (1) 1/130; (2) 3/131; (3) 3/122; (4) 1/131 Nausea: (1) 3/130; (2) 3/131; (3) 1/122; (4) 5/131 Abdominal pain: (1) 6/130; (2) 1/131; (3) 6/122; (4) 4/131 Vomiting: (1) 0/130; (2) 0/131; (3) 0/122; (4) 4/131 Tachycardia: (1) 7/130; (2) 2/131; (3) 1/122; (4) 2/131 Anxiety: (1) 3/130; (2) 1/131; (3) 0/122; (4) 0/131	(4) 0/131	(4) 2/131	quired treatment, 2 lost to follow-up, 17 did not report sufficient attacks
Dodick 2002	Protocol CL13 (1) Sumatriptan 100 mg, n = 193 (2) Almotriptan 12.5 mg, n = 183	Yes	No data	No data	No data	No data	No data

(Continued)

	(3) Placebo, n = 99						
Dowson 2002	(1) Sumatriptan 100 mg, n = 194 (2) Almotriptan 12.5 mg, n = 184 (3) Almotriptan 25 mg, n = 191 (4) Placebo, n = 99	Yes	Within 24 hours: (1) 43/194 (2) 16/184 (3) 35/191 (4) 6/99	Occurring in more than 2% of participants in any treatment group: Back pain: (1) 4/194; (2) 2/184; (3) 1/191; (4) 0/99 Fatigue: (1) 11/194; (2) 1/184; (3) 2/191; (4) 0/99 Paraesthesia: (1) 6/194; (2) 1/184; (3) 2/191; (4) 1/99 Dizziness: (1) 4/194; (2) 0/184; (3) 4/191; (4) 2/99 Somnolence: (1) 4/194; (2) 1/184; (3) 3/191; (4) 0/99	No data	(1) 0/194 (2) 0/184 (3) 0/191 (4) 0/99	(1) 1/194 (protocol violation) (2) 1/184 (protocol violation) (3) 6/191 (use of prohibited medication and protocol violation) (4) 0/99
Ensink 1991	(1) Sumatriptan 100 mg, n = 148 (2) Placebo, n = 84)	Yes	Within 24 hours: (1) 57/149 (2) 19/84	Most commonly reported adverse events: Nausea and/or vomiting: (1) 12/149; (2) 5/84 Malaise/fatigue: (1) 12/149; (2) 2/84 Disturbance of taste: (1) 10/149; (2) 3/84 Dizziness/vertigo: (1) 7/149; (2) 2/84 Headache: (1) 3/149; (2) 4/84 Chest symptoms: (1) 6/149; (2) 1/84	No data	(1) 2/149 (2) 1/84	1 excluded from efficacy analysis due to protocol violation

(Continued)

				Weakness: (1) 4/149; (2) 1/84			
Freitag 2001	(1) Sumatriptan 25 mg (+ additional dose of 25 mg at 2 h), n = 61 (2) Isometheptene combination 2 doses (+ additional single doses at 1, 2 and 3 h), n = 65	No	Within 24 hours: Drug-related (1) 11/61 (2) 13/65	Abdominal pain or cramps: (1) 1/61; (2) 2/65 Nausea: (1) 1/61; (2) 2/65 Diarrhoea: (1) 1/61; (2) 0/65 Lightheadedness: (1) 3/61; (2) 4/65 Sleepiness: (1) 3/61; (2) 2/65 Dry mouth: (1) 3/61; (2) 1/65 Heat flashes: (1) 0/61; (2) 1/65 Head pressure: (1) 2/61; (2) 0/65 Tremor: (1) 1/61; (2) 0/65 Sweating: (1) 1/61; (2) 0/65 Palpitations: (1) 0/61; (2) 1/65 Chest pain: (1) 2/61; (2) 0/65	No data	No data	11 other withdrawals: 7 due to failure to treat within allotted time frame, 2 lost to follow-up, 1 for protocol violation and 1 due to vomiting immediately after taking drug

(Continued)

				Enlarged thyroid: (1) 0/61; (2) 1/65 Sore throat: (1) 2/61; (2) 0/65 Laryngitis: (1) 1/61; (2) 0/65 Bruises: (1) 1/61; (2) 0/65 Stiff neck: (1) 1/61; (2) 0/65 Drug taste: (1) 1/61; (2) 0/65 Confusion: (1) 0/61; (2) 1/65			
Gallagher 2000	(1) Sumatriptan 25 mg, n = 336 (306 for efficacy) (2) Sumatriptan 50 mg, n = 338 (306 for efficacy) (3) Zolmitriptan 2.5 mg, n = 327 (295 for efficacy) (4) Zolmitriptan 5 mg, n = 337 (305 for efficacy)	Yes	Within 24 hours: Attack 1 (1) 69/336 (2) 99/338 (3) 91/327 (4) 111/337	Infection: (1) 6/336; (2) 19/338; (3) 19/327; (4) 14/337 Tightness: (1) 3/336; (2) 9/338; (3) 7/327; (4) 22/337 Nausea: (1) 14/336; (2) 25/338; (3) 23/327; (4) 38/337 Vomiting: (1) 13/336; (2) 20/338; (3) 12/327; (4) 14/337 Dizziness: (1) 15/336; (2) 17/338; (3) 20/327; (4) 27/337 Paraesthesia: (1) 12/336; (2) 15/338; (3) 16/327; (4) 27/337	10 (groups not reported)	(1) 9/336 (2) 7/338 (3) 6/327 (4) 12/337	No data

(Continued)

				Somnolence: (1) 12/336; (2) 13/338; (3) 14/327; (4) 26/337 Pharyngitis: (1) 17/336; (2) 14/338; (3) 23/327; (4) 26/337			
Geraud 2000	(1) Sumatriptan 100 mg, n = 504 (2) Zolmitriptan 5 mg, n = 498 (3) Placebo, n = 56	No	Probably within 24 hours: (1) 279/492 (2) 287/491 (3) 13/56	With an incidence of at least 5%: Asthenia: (1) 53/492; (2) 53/491; (3) 3/56 Dizziness/vertigo: (1) 46/492; (2) 44/491; (3) 1/56 Somnolence: (1) 29/492; (2) 37/491; (3) 2/56 Paraesthesia: (1) 33/492; (2) 29/491; (3) 0/56 Heaviness other than chest or neck: (1) 27/492; (2) 29/491; (3) 0/56 Nausea: (1) 35/492; (2) 30/491; (3) 1/56 Warm sensation: (1) 29/492; (2) 24/491; (3) 1/56 Neck pain: (1) 24/492; (2) 17/491; (3) 1/56	No drug related serious AEs	No data	No data
GL/MIG/001/92	(1) Sumatriptan 100 mg, n = 305 (2) Paracetamol 1000 mg + metoclopramide 10 mg, n = 302	Yes	Collected over > 24 hours (1) 162/305 (2) 98/302	Dizziness: (1) 22/305; (2) 13/302 Nausea: (1) 44/305; (2) 5/302	No useable data	(1) 18/305 (2) 5/302	Other withdrawals: (1) 35/305 (2) 42/302

(Continued)

	Numbness of extremities: (1) 2/305 (2) 0/302 Pins and needles through whole body: (1) 2/305; (2) 0/302 Anxiety: (1) 1/305; (2) 0/302 Backache: (1) 1/305; (2) 0/302 Chest pain: (1) 1/305; (2) 0/302 Feeling of heaviness in head: (1) 1/305; (2) 0/302 Hot sweats: (1) 1/305; (2) 0/302 Sweaty: (1) 8/305; (2) 0/302 Vomiting: (1) 7/305; (2) 6/302 Warm sensation: (1) 1/305; (2) 0/302 Weakness: (1) 6/305; (2) 1/302 Diarrhoea: (1) 3/305; (2) 5/302 Headache: (1) 5/305; (2) 6/302	Withdrawal due to lack of efficacy: (1) 0/305 (2) 8/302

(Continued)

				Drowsiness: (1) 7/305; (2) 5/302 Dyspepsia: (1) 5/305; (2) 0/302 Tiredness: (1) 4/305; (2) 9/302			
GL/MIG/001A/92	(1) Sumatriptan 100 mg, n = 348 (2) Paracetamol 1000 mg + metoclopramide 10 mg, n = 373	No	Collected over > 24 hours (1) 142/348 (2) 93/373	Chest pain: (1) 4/348; (2) 0/373 Nausea: (1) 30/348; (2) 6/373 Cervicalgia: (1) 3/348; (2) 0/373 Headache: (1) 2/348; (2) 2/373 Dizziness: (1) 24/348; (2) 9/373 Sweaty: (1) 2/348; (2) 0/373 Diarrhoea: (1) 5/348; (2) 4/373 Vomiting: (1) 11/348; (2) 3/373 Cold sensation: (1) 1/348; (2) 0/373 Feeling of heaviness: (1) 7/348; (2) 0/373	No useable data	(1) 13/348 (2) 8/373	Other withdrawals: (1) 95/348 (2) 92/373 Withdrawal due to lack of efficacy: (1) 11/347 (2) 11/373

(Continued)

				Pins and needles in arms: (1) 1/348; (2) 0/373 Tightness in chest: (1) 1/348; (2) 0/373 Abdominal pain: (1) 0/348; (2) 1/373 Anxiety states: (1) 0/348; (2) 1/373			
GL/MIG/002	(1) Sumatriptan 100 mg, n = 374 (2) Migraleve (buclizine hydrochloride 12.5 mg + paracetamol 1000 mg + codeine phosphate 16 mg), n = 378	Yes	Collected over > 24 hours (1) 183/374 (2) 127/378	Dizziness: (1) 31/374; (2) 16/378 Nausea: (1) 46/374; (2) 22/378 Headache: (1) 31/374; (2) 55/378 Tiredness: (1) 8/374; (2) 11/378 Dyspepsia: (1) 7/374; (2) 5/378 Cervicalgia: (1) 5/374; (2) 7/378 Drowsiness: (1) 3/374; (2) 6/378 Sweaty: (1) 2/374; (2) 6/278 Vomiting: (1) 2/374; (2) 7/378	No useable data	(1) 18/374 (2) 5/378	Other withdrawals: (1) 27/374 (2) 27/378 Withdrawal due to lack of efficacy: (1) 6/374 (2) 7/378

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				Weakness: (1) 2/374; (2) 0/378 Abdominal ache: (1) 1/374; (2) 0/378 Feeling of heaviness: (1) 1/374; (2) 0/378 Numbness in body: (1) 1/374; (2) 0/378 Chest pain: (1) 0/374; (2) 1/378			
GL/MIG/002A	(1) Sumatriptan 100 mg, n = 342 (2) Migraleve (buclizine hydrochloride 12.5 mg + paracetamol 1000 mg + codeine phosphate 16 mg), n = 332	No	Collected over > 24 hours (1) 146/342 (2) 95/332	Dizziness: (1) 24/342; (2) 19/332 Nausea: (1) 20/342; (2) 11/332 Headache: (1) 15/342; (2) 9/332 Tiredness: (1) 13/342; (2) 3/332 Drowsiness: (1) 6/342; (2) 2/332 Vomiting: (1) 5/342; (2) 4/332 Hot: (1) 4/342; (2) 4/332 Backache: (1) 3/342; (2) 3/332	No useable data	(1) 15/342 (2) 7/332	Other withdrawals: (1) 58/342 (2) 52/332 Withdrawals due to lack of efficacy: (1) 4/342 (2) 8/332

(Continued)

				Sweaty: (1) 4/342; (2) 5/332 Chest pain: (1) 1/342; (2) 1/332 Abdominal pain: (1) 1/342; (2) 0/332 Flushing of face: (1) 1/342; (2) 0/332 Heaviness in arm/leg: (1) 1/342; (2) 0/332 Palpitations: (1) 0/342; (2) 1/332			
GL/MIG/009	(1) Sumatriptan 100 mg, n = 255 (2) Migril (ergotamine tartrate 2 mg + cyclizine hydrochloride 50 mg + caffeine hydrate 100 mg), n = 258	Yes	Within 24 hours: (1) 75/255 (2) 68/258	Most frequent adverse events: Neck stiffness: (1) 17/255; (2) 0/258 Nausea: (1) 11/255; (2) 22/258 Dizziness: (1) 10/255; (2) 14/258 Diarrhoea: (1) 9/255; (2) 3/258 Vomiting: (1) 4/255; (2) 12/258 Light-headedness: (1) 7/255; (2) 6/258 Tiredness:	(1) 1/255 (2) 0/258	(1) 14/255 (2) 13/258	Other withdrawals: (1) 26/255 (2) 29/258 Withdrawals due to lack of efficacy: (1) 1/255 (2) 5/258

(Continued)

				(1) 7/255; (2) 4/258 Drowsiness: (1) 5/255; (2) 15/258 Sore throat: (1) 5/255; (2) 2/258 Vertigo: (1) 5/255; (2) 1/258			
Goadsby 1991	Number of attacks in efficacy population: (1) Sumatriptan 100 mg, n = 94 (2) Placebo, n = 94	No	No data	No data	No data	No data	No data
Goadsby 2000	(1) Sumatriptan 100 mg, n = 129 (2) Eletriptan 20 mg, n = 144 (3) Eletriptan 40 mg, n = 136 (4) Eletriptan 80 mg, n = 141 (5) Placebo, n = 142	Yes	Within 24 hours: (1) 52/129 (2) 49/144 (3) 48/136 (4) 72/141 (5) 24/142	Events with ≥ 4% incidence: Asthenia: (1) 4/129; (2) 3/144; (3) 4/136; (4) 14/141; (5) 0/142 Drowsiness: (1) 6/129; (2) 3/144; (3) 1/136; (4) 6/141; (5) 2/142 Nausea: (1) 4/129; (2) 4/144; (3) 2/136; (4) 10/141; (5) 1/142 Dizziness: (1) 5/129; (2) 3/144; (3) 5/136; (4) 6/141; (5) 1/142 Paraesthesia: (1) 7/129; (2) 6/144; (3) 3/136; (4) 11/141; (5) 2/142	None after eletriptan treatment, no other details reported	(1) 1/129 (2) 2/144 (3) 0/136 (4) 0/141 (5) 1/142	Other withdrawals: (1) 3/129 (2) 1/144 (3) 2/136 (4) 5/141 (5) 2/142

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Goldstein 1998	(1) Sumatriptan 25 mg, n = 563 (2) Sumatriptan 50 mg, n = 566 (3) Rizatriptan 5 mg, n = 557 (4) Rizatriptan 10 mg, n = 567 (5) Placebo, n = 141	No	Within 24 hours: Attack 1 (1) 137/297 (2) 134/291 (3) 129/294 (4) 137/305 (5) 50/142	Incidence ≥ 5% in any 1 treatment group: Asthenia/fatigue: (1) 9/297; (2) 17/291; (3) 12/294; (4) 9/305; (5) 1/142 Chest pain: (1) 15/297; (2) 9/291; (3) 9/294; (4) 6/305; (5) 0/142 Dizziness: (1) 12/297; (2) 26/291; (3) 26/294; (4) 34/305; (5) 7/142 Dry mouth: (1) 15/297; (2) 15/291; (3) 21/294; (4) 15/305; (5) 4/142 Headache: (1) 12/297; (2) 17/291; (3) 6/294; (4) 6/305; (5) 7/142 Nausea: (1) 15/297; (2) 17/291; (3) 12/294; (4) 15/305; (5) 3/142 Paraesthesia: (1) 12/297; (2) 9/291; (3) 9/294; (4) 15/305; (5) 1/142 Somnolence: (1) 15/297; (2) 17/291; (3) 12/294; (4) 21/305; (5) 6/142	No drug-related serious AEs	Attack 1 (1) 2/297 (2) 1/291 (3) 4/294 (4) 0/297 (5) 0/142	No data
Goldstein 2005	(1) Sumatriptan 50 mg, n = 67 (2) Acetaminophen 1000 mg + aspirin 1000 mg + caffeine	No	No data	No useable data - adverse events reported by body system rather than individually	(1) 0/67 (2) 0/69 (3) 0/35	No data	No data

(Continued)

	260 mg combination, n = 69 (3) Placebo, n = 35						
Gruffyd-Jones 2001	(1) Sumatriptan 50 mg, n = 555 (2) Zolmitriptan 2.5 mg, n = 551 (3) Zolmitriptan 5 mg, n = 560	Yes	Within 24 hours: (1) 191/555 (2) 192/551 (3) 211/560	Occurring in ≥ 4% of participants in any treatment group: Asthenia: (1) 25/555; (2) 29/551; (3) 37/560 Paraesthesia: (1) 30/555; (2) 29/551; (3) 29/560 Tightness: (1) 17/555; (2) 19/551; (3) 28/560 Dizziness: (1) 28/555; (2) 19/551; (3) 32/560 Somnolence: (1) 25/555; (2) 17/551; (3) 28/560	(1) 0/555 (2) 0/551 (3) 0/560	(1) 15/555 (2) 15/551 (3) 19/560	Other withdrawals: (1) 192/597 (2) 192/597 (3) 187/593
Havanka 2000	(1) Sumatriptan 100 mg, n = 98 (2) Naratriptan 1 mg, n = 85 (3) Naratriptan 2.5 mg, n = 87 (4) Naratriptan 5 mg, n = 93 (5) Naratriptan 7.5 mg, n = 93 (6) Naratriptan 10 mg, n = 96 (7) Placebo, n = 91	No	Within 24 hours: (1) 25/98 (2) 17/85 (3) 18/87 (4) 30/93 (5) 34/93 (6) 34/96 (7) 21/91	Most common adverse events: Malaise/fatigue: (1) 4/98; (2) 2/85; (3) 1/87; (4) 3/93; (5) 10/93; (6) 11/96; (7) 5/91 Nausea: (1) 1/98; (2) 0/85; (3) 3/87; (4) 4/93; (5) 4/93; (6) 4/96; (7) 1/91	No data	(1) 0/98 (2) 0/85 (3) 0/87 (4) 0/93 (5) 0/93 (6) 0/96 (7) 0/91	No data

(Continued)

Ishkanian 2007	(1) Sumatriptan 50 mg, n = 108 (2) Placebo, n = 108	No	Probably within 24 hours: (1) 21/108 (2) 12/108	Most common study drug-related AEs: Dizziness: (1) 5/108; (2) 1/107 Nausea: (1) 3/108; (2) 2/107 Other pressure/tightness: (1) 4/108; (2) 0/107 Temperature sensations: (1) 2/108; (2) 0/107	(1) 0/108 (2) 0/108	No data	1 excluded from efficacy analysis due to failure to return patient diary
Jelinski 2006	(1) Sumatriptan 50 mg, n = 126 (2) Sumatriptan 100 mg, n = 126 (3) Placebo, n = 109	Yes	Within 24 hours: Drug-related (1) 21/126 (2) 28/126 (3) 3/109	Most frequent adverse events: Nausea: (1) 3/126; (2) 5/127; (3) 1/111 Dizziness: (1) 2/126; (2) 4/127; (3) 2/111 Tingling: (1) 2/126; (2) 3/127; (3) 0/111 Chest tightness: (1) 0/126; (2) 3/127; (3) 1/111 Fatigue: (1) 6/126; (2) 2/127; (3) 1/111 Hot flushes: (1) 2/126; (2) 2/127; (3) 0/111 Tightness of throat: (1) 1/126; (2) 2/127; (3) 0/111 Weakness:	(1) 0/126 (2) 0/126 (3) no data	No data	3 excluded due to loss at follow-up

(Continued)

				(1) 1/126; (2) 2/127; (3) 0/111 Palpitations: (1) 2/126; (2) 0/127; (3) 0/111 Somnolence: (1) 2/126; (2) 0/127; (3) 0/111 Neck pain: (1) 1/126; (2) 0/127; (3) 1/111 Chest pain: (1) 1/126; (2) 0/127; (3) 0/111 Drowsiness: (1) 1/126; (2) 0/127; (3) 0/111 Numbness: (1) 1/126; (2) 0/127; (3) 0/111 Anxiety: (1) 0/126; (2) 0/127; (3) 1/111			
Kaniecki 2006	(1) Sumatriptan 100 mg, n = 131 (2) Placebo, n = 127	Yes	Probably within 24 hours: Drug-related (1) 17/131 (2) 6/127	Reported in > 2% of participants: Nausea: (1) 9/131; (2) 4/127 Dizziness: (1) 5/131; (2) 0/127	(1) 0/131 (2) 0/127	No data	5 excluded from efficacy analysis as failed to provide post-baseline efficacy assessments 3 excluded from placebo treatment arm (no details reported)
Kolodny 2004	(1) Sumatriptan 25 mg, n = 554 (290 1st attack only)	No	Within 24 hours: Attack 1	With common AEs: Asthenia/fatigue:	No data	3 (groups not reported)	157 other discontinuations:

(Continued)

	(2) Sumatriptan 50 mg, n = 550 (287 1st attack only) (3) Rizatriptan 5 mg, n = 536 (288 1st attack only) (4) Rizatriptan 10 mg, n = 547 (294 1st attack only) (5) Placebo, n = 288	(1) 113/290 (2) 142/287 (3) 109/288 (4) 139/294 (5) 102/288	(1) 13/290; (2) 17/287; (3) 15/288; (4) 11/294; (5) 6/288 Chest pain: (1) 3/290; (2) 13/287; (3) 5/288; (4) 10/294; (5) 7/288 Diarrhoea: (1) 3/290; (2) 14/287; (3) 4/288; (4) 3/294; (5) 6/288 Dry mouth: (1) 13/290; (2) 18/287; (3) 11/288; (4) 18/294; (5) 19/288 Flushing: (1) 12/290; (2) 14/287; (3) 3/288; (4) 9/294; (5) 2/288 Nausea: (1) 12/290; (2) 19/287; (3) 13/288; (4) 17/294; (5) 12/288 Dizziness: (1) 17/290; (2) 30/287; (3) 19/288; (4) 25/294; (5) 13/288 Headache: (1) 9/290; (2) 12/287; (3) 8/288; (4) 6/294; (5) 1/288 Paraesthesia: (1) 10/290; (2) 10/287; (3) 6/288; (4) 13/294; (5) 2/288 Somnolence: (1) 11/290; (2) 18/287; (3) 17/288; (4) 23/294; (5) 13/288	94 did not have 2nd headache, 18 lost to follow-up, 13 withdrew from study, 14 were uncooperative, 18 discontinued due to lack of therapeutic response, need for concomitant medication, or inclusion/exclusion criteria not met

(Continued)

Kudrow 2005	(1) Sumatriptan 50 mg, n = 144 (2) Valdecoxib 20 mg, n = 137 (3) Valdecoxib 40 mg, n = 152 (4) Placebo, n = 141	Yes	Within 24 hours: (1) 45/141 (2) 32/133 (3) 42/149 (4) 41/140	Occurring in > 2% of dosed participants: Dry mouth: (1) 8/141; (2) 3/133; (3) 2/149; (4) 1/140 Nausea: (1) 6/141; (2) 3/133; (3) 3/149; (4) 2/140 Diarrhoea: (1) 5/141; (2) 2/133; (3) 3/149; (4) 0/140 Paraesthesia: (1) 5/141; (2) 4/133; (3) no data; (4) 2/140 Fatigue: (1) 4/141; (2) 2/133; (3) 4/149; (4) 4/140 Somnolence: (1) 3/141; (2) 4/133; (3) 4/149; (4) 3/140 Dizziness (excl. vertigo): (1) 3/141; (2) 3/133; (3) 7/149; (4) 4/140 Anxiety: (1) 3/141; (2) 0/133; (3) 1/149; (4) 0/140 Headache: (1) 1/141; (2) 2/133; (3) 2/149; (4) 3/140 Hypoaesthesia: (1) 1/141; (2) 2/133; (3) 1/149; (4) 3/140	No data	No data	Total withdrawals (possibly including AE withdrawals, but not specified): (1) 3/144 (2) 4/137 (3) 5/152 (4) 2/141
Latere 1991	(1) Sumatriptan (dispersible) 100 mg, n = 288 (2) Cafergot, n = 289	No	Within 24 hours: (1) 130/290 (2) 113/290	No useable data - no. of events rather than participants with event reported	(1) 2/290 (2) 0/290	(1) 6/290 (2) 9/290	No data

(Continued)

Lines 2001	(1) Sumatriptan 50 mg, n = 356 (2) Rizatriptan 5 mg, n = 349 (3) Placebo, n = 80	No	No data	No data	No data	No data	No data
Lipton 2000	Treated attacks: (1) Sumatriptan 50 mg, n = 870 (2) Placebo, n = 240	No	Within 24 hours: Attacks treated with drug-related AE (1) 83/1358 (2) 19/356	No data	1 (group not reported)	7 drug-related AE withdrawals (groups not reported)	62 excluded from efficacy analysis due to failure to treat (53), incomplete data (2) or non-compliance (7)
Matthew 2003	(1) Sumatriptan 100 mg, n = 831 (2) Eletriptan 40 mg, n = 822 (3) Placebo, n = 419	Yes	Within 7 days: (1) 314/849 (2) 259/835 (3) 146/429	Incidence ≥ 2%: Nausea: (1) 125/849; (2) 99/835; (3) 54/429 Vomiting: (1) 49/849; (2) 49/835; (3) 46/429 Photophobia: (1) 39/849; (2) 34/835; (3) 24/429 Asthenia: (1) 20/849; (2) 13/835; (3) 4/429 Chest symptoms: (1) 17/849; (2) 13/835; (3) 2/429 Paraesthesia: (1) 20/849; (2) 9/835; (3) 0/429	No drug-related serious AEs	No data	Total withdrawals (possibly including AE withdrawals, but not specified): (1) 1/849 (2) 3/835 (3) 0/429
Myllyla 1998	(1) Sumatriptan 100 mg (+ optional	Yes	No useable data	No useable data	No data	2 (groups not reported)	8 withdrawn due to lack of attacks

(Continued)

	dose of placebo after 1 h), n = 46 (2) Tolfenamic acid 200 mg (+ optional 2nd dose after 1 h), n = 47 (3) Placebo (+ optional dose of placebo after 1 h), n = 46						(groups not reported) 3 lost to follow-up
Nappi 1994	(1) Sumatriptan 100 mg, n = 158 (2) Placebo, n = 86	Yes	Within 24 hours: Participants receiving 1 dose only (1) 24/69 (2) 4/19	Reported by at least 4 sumatriptan-treated participants: Nausea and/or vomiting: (1) 12/162; (2) 6/88 Gastric symptoms: (1) 8/162; (2) 1/88 Malaise/fatigue: (1) 4/162; (2) 2/88 Abdominal discomfort: (1) 4/162; (2) 1/88	No data	(1) 8/162 (2) 2/88	6 excluded from efficacy analysis due to protocol violations
Nett 2003	(1) Sumatriptan 50 mg, n = 124 (2) Sumatriptan 100 mg, n = 122 (3) Placebo, n = 123	No	Probably within 24 hours: (1) 10/124 (2) 20/122 (3) 9/123	Reported by more than 2% of participants in any treatment group: Nausea: (1) 2/124; (2) 8/122; (3) 3/123 Paraesthesia: (1) 1/124; (2) 0/122; (3) 0/123 Dizziness: (1) 3/124; (2) 0/122; (3) 1/123 Malaise/fatigue:	(1) 0/124 (2) 0/122 (3) 0/123	(1) 0/124 (2) 0/122 (3) 0/123	48 excluded: 18 lost to follow-up, 22 did not treat, 2 protocol violations, 5 withdrew consent, 3 other

(Continued)

				(1) 0/124; (2) 0/122; (3) 1/123			
Patten 1991	(1) Sumatriptan (dispersible) 100 mg, n = 142 (2) Sumatriptan (dispersible) 200 mg, n = 140 (3) Sumatriptan (dispersible) 300 mg, n = 155 (4) Placebo, n = 101	No	No useable data	Chest symptoms: (1) 1/69; (2) 2/56; (3) 8/60; (4) 0/42 Heaviness/pressure/ warmth: (1) 3/69; (2) 9/56; (3) 6/60; (4) 2/42 Tingling/prickling: (1) 7/69; (2) 1/56; (3) 2/60; (4) 0/42 Drowsiness/sedation: (1) 2/69; (2) 2/56; (3) 4/60; (4) 1/42 Nausea/vomiting: (1) 6/69; (2) 8/56; (3) 8/60; (4) 2/42 Bitter taste: (1) 5/69; (2) 5/56; (3) 13/60; (4) 3/42	No data	(1) 2/69 (2) 7/46 (3) 11/60 (4) 1/42	No data
Pfaffenrath 1998	(1) Sumatriptan 25 mg, n = 303 (2) Sumatriptan 50 mg, n = 303 (3) Sumatriptan 100 mg, n = 298 (4) Placebo, n = 99	Yes	Within 24 hours: (1) 74/303 (2) 82/303 (3) 111/298 (4) 20/99	Incidence of ≥ 4% in any treatment group, after single dose only: Malaise/fatigue: (1) 9/303; (2) 8/303; (3) 15/298; (4) 1/99 Nausea/vomiting: (1) 7/303; (2) 18/303; (3) 13/298; (4) 2/99 Dizziness: (1) 5/303; (2) 4/303; (3) 14/298; (4) 2/99 Chest pressure/heaviness: (1) 3/303; (2) 11/303; (3) 9/298; (4) 0/99 Muscle pain: (1) 3/303; (2) 1/303; (3) 3/298; (4) 0/99	No data	(1) 2/303 (2) 3/303 (3) 8/298 (4) 1/99	88 other withdrawals: 21 due to lack of efficacy, 6 lost to follow-up, 20 due to protocol violation, 41 other

(Continued)

Pini 1999	(1) Sumatriptan 50 mg, n = 137 (106 for efficacy) (2) Placebo, n = 82 (61 for efficacy)	Yes	Within 24 hours: (1) 10/106 (2) 4/82	No useable data - adverse events reported by body system rather than individually	(1) 0/106 (2) 0/82	No data	Total withdrawals (possibly including AE withdrawals, but not specified): 12 (groups not given)
Pini 1995	(1) Sumatriptan 100 mg, n = 151 (2) Placebo, n = 87	No	Within 48 hours: Drug-related (1) 18/151 (2) 6/87	Occurring in over 1% of participants: Malaise/fatigue: (1) 7/151; (2) 0/87 Nausea and/or vomiting: (1) 5/151; (2) 1/87 Paraesthesia: (1) 3/151; (2) 1/87 Numbness: (1) 3/151; (2) 0/87 Throat symptoms/neck stiffness: (1) 3/151; (2) 0/87 Chest symptoms: (1) 2/151; (2) 8/87 Heaviness/pressure sensation: (1) 2/151; (2) 0/87	No data	No data	No data
Sandrini 2002	(1) Sumatriptan 50 mg, n = 181 (2) Sumatriptan 100 mg, n = 170 (3) Eletriptan 40 mg, n = 175	Yes	No data	Occurring in ≥ 5% in any treatment group: Asthenia: (1) 9/181; (2) 7/169; (3) 11/175; (4) 15/164; (5) 2/84 Nausea:	No drug-related serious AEs	(1) 1/181 (after 2 doses) (2) 2/170 (after 2 doses) (3) 2/175 (1 after 2 doses and the oth-	No data

(Continued)

	(4) Eletriptan 80 mg, n = 164 (5) Placebo, n = 84			(1) 9/181; (2) 8/169; (3) 5/175; (4) 15/164; (5) 2/84 Dizziness: (1) 11/181; (2) 5/169; (3) 11/175; (4) 15/164; (5) 2/84 Somnolence: (1) 2/181; (2) 3/169; (3) 12/175; (4) 6/164; (5) 2/84 Chest symptoms: (1) 2/181; (2) 0/169; (3) 1/175; (4) 7/164; (5) 2/84 Sweating: (1) 0/181; (2) 3/169; (3) 8/175; (4) 3/164; (5) 2/84		er after single dose) (4) 1/164 (after single dose) (5) 2/84	
Sandrini 2007	(1) Sumatriptan 50 mg, n = 139 (138 for efficacy) (2) Indoprocaf, n = 143	Yes	Within 24 hours: (1) 25/139 (2) 31/143	No data	(1) 1/139 (2) 0/143	(1) 1/139 (2) 3/143	1 excluded from efficacy analysis due to failure to return patient diary
Sargent 1995	(1) Sumatriptan 25 mg, n = 48 (2) Sumatriptan 50 mg, n = 46 (3) Sumatriptan 100 mg, n = 46 (4) Placebo, n = 47	No	Probably within 72 hours: (1) 15/48 (2) 17/46 (3) 15/46 (4) 14/47	Experienced by ≥ 3 participants in any treatment group: Nausea/vomiting: (1) 1/48; (2) 5/46; (3) 6/46; (4) 8/47 Mouth disorder: (1) 2/48; (2) 1/46; (3) 0/46; (4) 0/47 Dizziness/vertigo: (1) 1/48; (2) 3/46; (3) 2/46; (4) 2/47 Drowsiness/sedation: (1) 3/48; (2) 0/46; (3) 2/46; (4) 0/47	No data	(1) 0/48 (2) 0/46 (3) 0/46 (4) 0/47	No data

(Continued)

				Tingling: (1) 3/48; (2) 2/46; (3) 3/46; (4) 2/47 Chills: (1) 3/48; (2) 0/46; (3) 1/46; (4) 2/47			
Savani 1999	(1) Sumatriptan 50 mg, n = 331 (2) Placebo, n = 154	Yes	Within 24 hours: (1) 82/332 (2) 32/156	Experienced by 1% or more of participants in any treatment group: Paraesthesia: (1) 7/332; (2) 1/156 Numbness: (1) 5/332; (2) 1/156 Tingling: (1) 5/332; (2) 1/156 Warm or hot sensation: (1) 5/332; (2) 2/156 Feeling of tightness: (1) 4/332; (2) 1/156 Nausea or vomiting: (1) 14/332; (2) 4/156 Dizziness: (1) 12/332; (2) 3/156 Headache: (1) 3/332; (2) 2/156 Malaise and fatigue: (1) 7/332; (2) 1/156	1 (group not reported)	12 (groups not reported)	52 withdrawals: 5 due to lack of efficacy, 15 lost to follow-up, 32 for other reasons
Schulman 2003	(1) Sumatriptan 50 mg, n = 16	No	Within 24 hours:	No data	(1) 0/16 (2) 0/16	No data	No data

(Continued)

	(2) Sumatriptan 50 mg + metoclopramide 10 mg, n = 16		(1) 2/16 (2) 4/16				
Sheftell 2005	Study 1: (1) Sumatriptan (rapid-release) 50 mg, n = 494 (2) Sumatriptan (rapid-release) 100 mg, n = 488 (3) Placebo, n = 495 Study 2: (1) Sumatriptan (rapid-release) 50 mg, n = 496 (2) Sumatriptan (rapid-release) 100 mg, n = 485 (3) Placebo, n = 494	Yes	Within 7 days: Drug-related Study 1 (1) 40/494 (2) 57/488 (3) 17/495 Study 2 (1) 58/496 (2) 94/485 (3) 25/494	Reported in > 2% of participants in any treatment group: Nausea: Study 1 (1) 11/494; (2) 13/488; (3) 5/495 Study 2 (1) 10/496; (2) 16/485; (3) 5/494 Paraesthesia Study 1 (1) 4/494; (2) 3/488; (3) 0/495 Study 2 (1) 5/496; (2) 14/485; (3) 1/494	No drug related serious AEs	Study 1 (1) 0/494 (2) 0/488 (3) 0/495 Study 2 (1) 0/496 (2) 0/485 (3) 0/494	"Premature withdrawals": Study 1 (1) 72/556 (2) 67/551 (3) 75/558 Study 2 (1) 66/561 (2) 65/550 (3) 61/555
Smith 2005	(1) Sumatriptan 50 mg, n = 229 (2) Sumatriptan 50 mg, + naproxen 500 mg, n = 251 (3) Naproxen 500 mg, n = 250 (4) Placebo, n = 241	No	Within 24 hours: (1) 55/229 (2) 58/251 (3) 43/250 (4) 36/241	Reported in > 2% of participants in any treatment group: Chest tightness: (1) 2/229; (2) 4/250; (3) 5/251; (4) 3/242 Diarrhoea: (1) 4/229; (2) 6/250; (3) 0/251; (4) 3/242 Dizziness (not vertigo): (1) 11/229; (2) 4/250; (3) 9/251; (4) 8/242 Dry mouth: (1) 4/229; (2) 3/250; (3) 4/251; (4) 1/242 Fatigue:	(1) 0/229 (2) 0/251 (3) 0/250 (4) 0/241	No data	7 excluded from efficacy analysis for protocol violations

(Continued)

				(1) 1/229; (2) 0/250; (3) 5/251; (4) 0/242 Nausea aggravated: (1) 3/229; (2) 2/250; (3) 1/251; (4) 4/242 Paraesthesia: (1) 4/229; (2) 1/250; (3) 2/251; (4) 1/242 Somnolence: (1) 6/229; (2) 2/250; (3) 3/251; (4) 0/242 Tinnitus: (1) 4/229; (2) 4/250; (3) 6/251; (4) 2/242			
Spierings 2001	(1) Sumatriptan 50 mg, n = 582 (2) Almotriptan 12.5 mg, n = 591	Yes	Within 24 hours: (1) 113/582 (2) 90/591	Occurring in at least 1% of subjects: Chest pain: (1) 13/582; (2) 2/591 Headache: (1) 9/582; (2) 8/591 Vasodilation: (1) 8/582; (2) 6/591 Diarrhoea: (1) 3/582; (2) 6/591 Nausea: (1) 20/582; (2) 13/591 Dizziness: (1) 10/582; (2) 12/591 Paraesthesia: (1) 5/582; (2) 7/591 Somnolence: (1) 11/582; (2) 8/591	(1) 0/582 (2) 0/591	(1) 0/582 (2) 0/591	Other withdrawals: 8 withdrawn (4 from each group), no further details reported

(Continued)

				Palpitations: (1) 0/582; (2) 2/591			
Tfelt-Hansen 1995	(1) Sumatriptan 100 mg, n = 122 (2) Lysine acetylsalicylate 1620 mg + metoclopramide 10 mg, n = 137 (3) Placebo, n = 126	No	Within 24 hours: (1) 38/125 (2) 25/138 (3) 18/126	Nausea/vomiting: (1) 14/125; (2) 3/138; (3) 11/126 Somnolence: (1) 6/125; (2) 12/138; (3) 0/126 Fatigue/weakness: (1) 8/125; (2) 3/138; (3) 3/126 Abdominal pain: (1) 6/125; (2) 7/138; (3) 2/126 Constriction of throat/chest pain: (1) 6/125; (2) 0/138; (3) 0/126 Paraesthesia: (1) 6/125; (2) 0/138; (3) 0/126 Heaviness in lower limbs: (1) 5/125; (2) 0/138; (3) 0/126 Back or neck pain: (1) 4/125; (2) 0/138; (3) 0/126 Syncope: (1) 3/125; (2) 0/138; (3) 0/126 Vertigo/dizziness: (1) 3/125; (2) 1/138; (3) 1/126	1 (group not reported)	(1) 4/125 (2) 1/138 (3) 2/126	4 excluded from the efficacy analysis due to incomplete patient diary data
Tfelt-Hansen 1998	(1) Sumatriptan 100 mg, n = 388 (2) Rizatriptan 5 mg, n = 164	No	Within 24 hours: (1) 202/388 (2) 64/164	Reported in > 5% of participants: Somnolence: (1) 28/388; (2) 12/164; (3) 33/387; (4) 9/160	(1) 0/388 (2) 0/164 (3) 0/387	Drug-related (1) 1/388 (2) 0/164	7 other discontinuations: 2 lost to follow-up, 1 withdrew

(Continued)

	(3) Rizatriptan 10 mg, n = 387 (4) Placebo, n = 160		(3) 180/387 (4) 51/160	Dizziness: (1) 35/388; (2) 9/164; (3) 30/387; (4) 6/160 Asthenia/fatigue: (1) 32/388; (2) 4/164; (3) 30/387; (4) 6/160 Nausea: (1) 35/388; (2) 8/164; (3) 22/387; (4) 4/160 Vomiting: (1) 10/388; (2) 5/164; (3) 12/387; (4) 8/160 Abdominal pain: (1) 20/388; (2) 7/164; (3) 12/387; (4) 2/160 Chest pain: (1) 22/388; (2) 2/164; (3) 13/387; (4) 4/160	(4) 0/160	(3) 0/387 (4) 0/160	from study, 4 for protocol violations
Tfelt-Hansen 2006	(1) Sumatriptan 50 mg, n = 53 (2) Placebo, n = 48	Yes	Within 24 hours: (1) 27/53 (2) 7/48	No useable data - no. of individual adverse events not reported separately by treatment arm	No data	No data	2 withdrawals (one from each group) for protocol violations
Thomson 1992	(1) Sumatriptan 100 mg, n = 175 (2) Aspirin 900 mg + metoclopramide 10 mg, n = 183	No	Within 24 hours: (1) 74/175 (2) 53/183	Incidence ≥ 2%: Nausea and/or vomiting: (1) 18/175; (2) 14/183 Malaise/fatigue: (1) 11/175; (2) 6/183 Dizziness/vertigo: (1) 9/175; (2) 4/183 Disturbance of taste: (1) 8/175; (2) 4/183 Sweating:	No data	Drug-related (1) 5/175 (2) 0/183	3 excluded from efficacy analysis due to failure to return patient diary

(Continued)

(1) 7/175; (2) 1/183

Abdominal discomfort:

(1) 5/175; (2) 3/183

Throat symptoms:

(1) 6/175; (2) 2/183

Headache:

(1) 6/175; (2) 1/183

Chest symptoms:

(1) 4/175; (2) 1/183

Feeling of heaviness:

(1) 4/175; (2) 0/183

Neck pain/stiffness:

(1) 3/175; (2) 3/183

Paraesthesia:

(1) 3/175; (2) 1/183

Diarrhoea:

(1) 2/175; (2) 8/183

Tachycardia:

(1) 1/175; (2) 3/183

Gastroesophageal reflux:

(1) 1/175; (2) 3/183

Mouth/tongue disorder:

(1) 1/175; (2) 4/183

Drowsiness/sedation:

(1) 1/175; (2) 3/183

(Continued)

Visser 1996	(1) Sumatriptan 100 mg, n = 72 (2) Rizatriptan 10 mg, n = 89 (3) Rizatriptan 20 mg, n = 82 (4) Rizatriptan 40 mg, n = 121 (5) Placebo, n = 85	Yes	Within 24 hours: In participants taking only single dose (1) 15/33 (2) 23/48 (3) 31/46 (4) 66/80 (5) 5/14	Incidence ≥ 5% in any 1 treatment group after single dose only: Dizziness: (1) 1/33; (2) 4/48; (3) 14/46; (4) 29/80; (5) 1/14 Drowsiness: (1) 1/33; (2) 5/48; (3) 11/46; (4) 16/80; (5) 3/14 Asthenia/fatigue: (1) 1/33; (2) 2/48; (3) 6/46; (4) 14/80; (5) 0/14 Nausea: (1) 1/33; (2) 1/48; (3) 2/46; (4) 9/80; (5) 0/14 Paraesthesia: (1) 3/33; (2) 2/48; (3) 3/46; (4) 8/80; (5) 1/14 Dry mouth: (1) 1/33; (2) 1/48; (3) 5/46; (4) 7/80; (5) 0/14 Heaviness, regional: (1) 4/33; (2) 2/48; (3) 1/46; (4) 6/80; (5) 1/14 Chest pain: (1) 3/33; (2) 2/48; (3) 2/46; (4) 6/80; (5) 0/14 Mental acuity decreased: (1) 0/33; (2) 1/48; (3) 1/46; (4) 4/80; (5) 1/14 Abdominal pain: (1) 1/33; (2) 1/48; (3) 0/46; (4) 4/80; (5) 0/14 Stiffness: (1) 2/33; (2) 0/48; (3) 0/46; (4) 2/80; (5) 0/14 Headache:	(1) 0/72 (2) 0/89 (3) 1/82 (after 2 doses) (4) 0/121 (5) 0/85	(1) 0/72 (2) 0/89 (3) 0/82 (4) 0/121 (5) 0/85	No other withdrawals after taking study medication

(Continued)

				(1) 2/33; (2) 0/48; (3) 6/46; (4) 2/80; (5) 0/14 Neck pain: (1) 2/33; (2) 0/48; (3) 1/46; (4) 0/80; (5) 0/14			
Winner 2003	Study 1: (1) Sumatriptan 50 mg, n = 122 (2) Sumatriptan 100 mg, n = 115 (3) Placebo, n = 117 Study 2: (1) Sumatriptan 50 mg, n = 111 (2) Sumatriptan 100 mg, n = 107 (3) Placebo, n = 119	Yes	Within 24 hours: Study 1 (1) 22/122 (2) 22/115 (3) 9/117 Study 2 (1) 10/111 (2) 13/107 (3) 7/119	Occurring at a rate of 3% or greater: Study 1 Nausea: (1) 4/122; (2) 3/116; (3) 1/117 Dizziness: (1) 4/122; (2) 2/116; (3) 0/117 Somnolence: (1) 0/122; (2) 3/116; (3) 0/117 Paraesthesia: (1) 2/122; (2) 3/116; (3) 2/117 Other pressure/tightness: (1) 2/122; (2) 3/116; (3) 0/117 Study 2 Dizziness: (1) 0/111; (2) 3/107; (3) 1/120	Study 1 (1) 0/122 (2) 0/115 (3) 0/117 Study 2 (1) 0/111 (2) 0/107 (3) 0/119	No data	Total withdrawals (possibly including AE withdrawals): Study 1 (1) 16/138 (2) 23/138 (3) 24/141 Study 2 (1) 11/122 (2) 21/127 (3) 14/133

Appendix 8. Breakdown of individual adverse event groups

We used the following groupings of individual adverse events in all four reviews of sumatriptan whenever it was possible to combine studies for analysis (all routes of administration except rectal).

Malaise/fatigue/asthenia:

- Malaise/fatigue
- Fatigue
- Malaise and fatigue
- Asthenia/fatigue
- Fatigue/weakness
- Asthenia
- Weakness

Dizziness/vertigo:

- Dizziness/vertigo
- Dizziness
- Dizziness (excl. vertigo)
- Dizziness (not vertigo)

Nausea/vomiting:

- Nausea/vomiting
- Nausea
- Vomiting
- Nausea and vomiting

Disorder of mouth/disturbance of taste:

- Disorder of mouth/tongue
- Mouth disorder
- Dry mouth
- Disturbance of taste
- Bad taste
- Drug taste

Chest pain/symptoms:

- Chest pressure/heaviness
- Chest tightness
- Chest discomfort
- Chest pain
- Chest symptoms
- Constriction of throat/chest pain
- Tightness of throat

Heat sensations/flushing:

- Warm/hot sensation
- Flushing
- Vasodilation
- Heat flashes
- Warm sensation
- Temperature sensations
- Hot flush
- Burning sensation

Palpitations/tachycardia:

- Palpitations
- Tachycardia

Diarrhoea:

- Diarrhoea

Feeling of tightness/heaviness:

- Feeling of heaviness
- Heaviness other than chest or neck
- Feeling of heaviness in head
- Heaviness/pressure sensation
- Heaviness in lower limbs
- Heaviness, regional
- Head pressure
- Tightness
- Other pressure/tightness

Sweating:

- Sweating

Abdominal pain/discomfort/dyspepsia:

- Abdominal discomfort
- Abdominal pain
- Abdominal pain or cramps
- Dyspepsia
- Gastric symptoms
- Gastroesophageal reflux

Paraesthesia/numbness:

- Paraesthesia
- Tingling
- Numbness/paraesthesia/tingling
- Numbness

Headache:

- Headache

Drowsiness/somnolence:

- Drowsiness/sedation
- Somnolence
- Sleepiness
- Drowsiness

Anxiety:

- Anxiety

Neck/back pain:

- Neck pain/stiffness
- Neck pain
- Back or neck pain

- Back pain

Disorder of nasal cavity/sinuses:

- Disorder of nasal cavity/sinuses
- Nasal discomfort
- Nasal stuffiness
- Wet nostrils

Throat symptoms

- Throat symptoms
- Throat discomfort

Injection-site reaction:

- Injection-site reaction
- Application site reaction

Appendix 9. Specific adverse events: sumatriptan versus active comparators

Summary of results E: Number of participants experiencing specific adverse events within 24 hours of study treatment

	Studies	Participants treated	Treatment (%)	Comparator (%)	Relative risk (95% CI)	NNH (95% CI)
Malaise/fatigue/asthenia						
Sumatriptan 25 mg versus rizatriptan 5 mg	2	1169	4	5	0.81 (0.47 to 1.4)	Not calculated
Sumatriptan 25 mg versus rizatriptan 10 mg	2	1186	4	3	1.1 (0.62 to 2.0)	Not calculated
Sumatriptan 50 mg versus rizatriptan 5 mg	2	1160	6	5	1.3 (0.78 to 2.1)	Not calculated
Sumatriptan 50 mg verus rizatriptan 10 mg	2	1177	6	3	1.8 (1.0 to 3.0)	Not calculated
Sumatriptan 100 mg versus eletriptan 40 mg	2	609	4	5	0.76 (0.36 to 1.6)	Not calculated
Sumatriptan 100 mg versus eletriptan 80 mg	2	603	4	10	0.39 (0.20 to 0.76)	-17 (-10 to -53)
Sumatriptan 100 mg versus ASA 900 mg + MCP 10 mg	2	621	6	3	2.3 (1.0 to 4.9)	Not calculated
Sumatriptan 100 mg versus rizatriptan 10 mg	2	856	8	7	1.1 (0.66 to 1.7)	Not calculated
Dizziness/vertigo						
Sumatriptan 25 mg versus rizatriptan 5 mg	2	1169	5	8	0.64 (0.41 to 1.0)	Not calculated

(Continued)

Sumatriptan 25 mg versus rizatriptan 10 mg	2	1186	5	10	0.50 (0.33 to 0.77)	-20 (-13 to -51)
Sumatriptan 50 mg versus rizatriptan 5 mg	2	1160	10	8	1.3 (0.86 to 1.8)	Not calculated
Sumatriptan 50 mg versus rizatriptan 10 mg	2	1177	10	10	0.98 (0.69 to 1.4)	Not calculated
Sumatriptan 100 mg versus eletriptan 40 mg	2	609	3	5	0.65 (0.30 to 1.4)	Not calculated
Sumatriptan 100 mg versus eletriptan 80 mg	2	603	3	7	0.48 (0.23 to 1.0)	Not calculated
Sumatriptan 100 mg versus ASA 900 mg + MCP 10 mg	2	621	4	2	2.5 (0.91 to 7.1)	Not calculated
Sumatriptan 100 mg versus rizatriptan 10 mg	2	856	9	8	1.1 (0.69 to 1.7)	Not calculated
Nausea/vomiting						
Sumatriptan 25 mg versus rizatriptan 5 mg	2	1169	5	4	1.1 (0.63 to 1.8)	Not calculated
Sumatriptan 25 mg versus rizatriptan 10 mg	2	1186	5	5	0.86 (0.52 to 1.4)	Not calculated
Sumatriptan 50 mg versus rizatriptan 5 mg	2	1160	6	4	1.5 (0.88 to 2.4)	Not calculated
Sumatriptan 50 mg versus rizatriptan 10 mg	2	1177	6	5	1.2 (0.73 to 1.9)	Not calculated
Sumatriptan 100 mg versus eletriptan 40 mg	2	609	4	2	1.8 (0.71 to 4.5)	Not calculated
Sumatriptan 100 mg versus eletriptan 80 mg	2	603	4	8	0.49 (0.25 to 0.95)	-24 (-13 to -270)
Sumatriptan 100 mg versus ASA 900 mg + MCP 10 mg	2	621	11	5	2.0 (1.1 to 3.5)	19 (10 to 91)
Sumatriptan 100 mg versus rizatriptan 10 mg	2	856	9	5	1.6 (0.95 to 2.6)	Not calculated
Mouth disorder/disturbance of taste						
Sumatriptan 25 mg versus rizatriptan 5 mg	2	1169	5	5	0.87 (0.53 to 1.4)	Not calculated
Sumatriptan 25 mg versus rizatriptan 10 mg	2	1186	5	6	0.87 (0.53 to 1.4)	Not calculated

(Continued)

Sumatriptan 50 mg versus rizatriptan 5 mg	2	1160	6	5	1.0 (0.65 to 1.7)	Not calculated
Sumatriptan 50 mg versus rizatriptan 10 mg	2	1177	6	6	1.0 (0.65 to 1.7)	Not calculated
Chest pain/symptoms						
Sumatriptan 25 mg versus rizatriptan 5 mg	2	1169	3	2	1.3 (0.64 to 2.5)	Not calculated
Sumatriptan 25 mg versus rizatriptan 10 mg	2	1186	3	3	1.2 (0.59 to 2.2)	Not calculated
Sumatriptan 50 mg versus rizatriptan 5 mg	2	1170	4	2	1.6 (0.83 to 3.1)	Not calculated
Sumatriptan 50 mg versus rizatriptan 10 mg	2	1177	4	3	1.4 (0.75 to 2.7)	Not calculated
Sumatriptan 100 mg versus ASA 900 mg + MCP 10 mg	2	621	3	0	7.5 (1.4 to 41)	33 (19 to 120)
Sumatriptan 100 mg versus rizatriptan 10 mg	2	856	6	3	1.7 (0.93 to 3.3)	Not calculated
Feeling of heaviness/tightness						
Sumatriptan 100 mg versus ASA 900 mg + MCP 10 mg	2	621	3	0	11 (1.4 to 83)	33 (19 to 110)
Paraesthesia/numbness						
Sumatriptan 25 mg versus rizatriptan 5 mg	2	1169	4	3	1.5 (0.76 to 2.8)	Not calculated
Sumatriptan 25 mg versus rizatriptan 10 mg	2	1186	4	5	0.80 (0.46 to 1.4)	Not calculated
Sumatriptan 50 mg versus rizatriptan 5 mg	2	1160	3	3	1.3 (0.65 to 2.5)	Not calculated
Sumatriptan 50 mg versus rizatriptan 10 mg	2	1177	3	5	0.70 (0.40 to 1.3)	Not calculated
Sumatriptan 100 mg versus ASA 900 mg + MCP 10 mg	2	621	3	0	6.8 (1.2 to 38)	37 (21 to 170)
Headache						
Sumatriptan 25 mg versus rizatriptan 5 mg	2	1169	4	2	1.5 (0.76 to 2.9)	Not calculated
Sumatriptan 25 mg versus rizatriptan 10 mg	2	1186	4	2	1.8 (0.89 to 3.6)	Not calculated

(Continued)

Sumatriptan 50 mg versus rizatriptan 5 mg	2	1160	5	2	2.1 (1.1 to 3.9)	38 (21 to 230)
Sumatriptan 50 mg versus rizatriptan 10 mg	2	1183	5	2	2.5 (1.3 to 4.8)	34 (20 to 114)
Drowsiness/somnolence						
Sumatriptan 25 mg versus rizatriptan 5 mg	2	1169	4	5	0.89 (0.53 to 1.5)	Not calculated
Sumatriptan 25 mg versus rizatriptan 10 mg	2	1186	4	7	0.60 (0.38 to 0.97)	-34 (-18 to -410)
Sumatriptan 50 mg versus rizatriptan 5 mg	2	1160	6	5	1.2 (0.75 to 2.0)	Not calculated
Sumatriptan 50 mg versus rizatriptan 10 mg	2	1177	6	7	0.82 (0.54 to 1.3)	Not calculated
Sumatriptan 100 mg versus eletriptan 40 mg	2	609	3	4	0.72 (0.31 to 1.7)	Not calculated
Sumatriptan 100 mg versus eletriptan 80 mg	2	603	3	4	0.78 (0.34 to 1.8)	Not calculated
Sumatriptan 100 mg versus ASA 900 mg + MCP 10 mg	2	621	2	5	0.51 (0.21 to 1.2)	Not calculated
Sumatriptan 100 mg versus rizatriptan 10 mg	2	856	7	9	0.79 (0.49 to 1.3)	Not calculated
Abdominal pain/discomfort/dyspepsia						
Sumatriptan 100 mg versus ASA 900 mg + MCP 10 mg	2	621	4	3	1.2 (0.51 to 2.8)	Not calculated
Sumatriptan 100 mg versus rizatriptan 10 mg	2	856	5	3	1.7 (0.84 to 3.3)	Not calculated
Neck/back pain						
Sumatriptan 100 mg versus ASA 900 mg + MCP 10 mg	2	621	2	1	2.3 (0.65 to 8.0)	Not calculated

Appendix 10. L'Abbé plots for sumatriptan 50 mg versus placebo

L'Abbé plots for sumatriptan 50 mg versus placebo for the outcomes headache relief at two hours (Figure 8), pain-free at two hours (Figure 9), and sustained pain-free at 24 hours (Figure 10) show consistency in response across studies for these outcomes.

Figure 8. L'Abbé plot showing results for sumatriptan 50 mg versus placebo for headache relief at 2 hours. Each circle represents a different study; size of circle is proportional to size of study; diagonal is line of equivalence

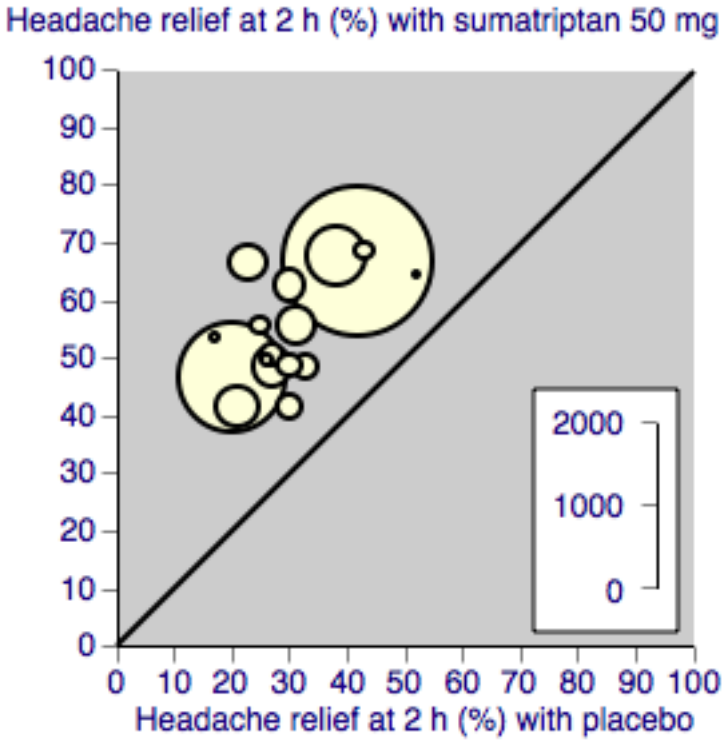


Figure 9. L'Abbé plot showing results for sumatriptan 50 mg versus placebo for pain-free at 2 hours. Each circle represents a different study; size of circle is proportional to size of study; diagonal is line of equivalence

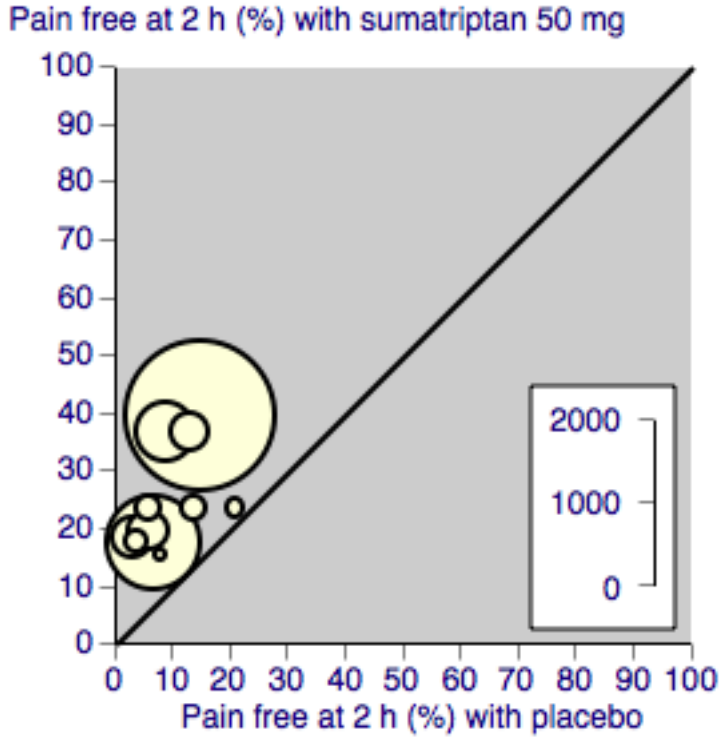
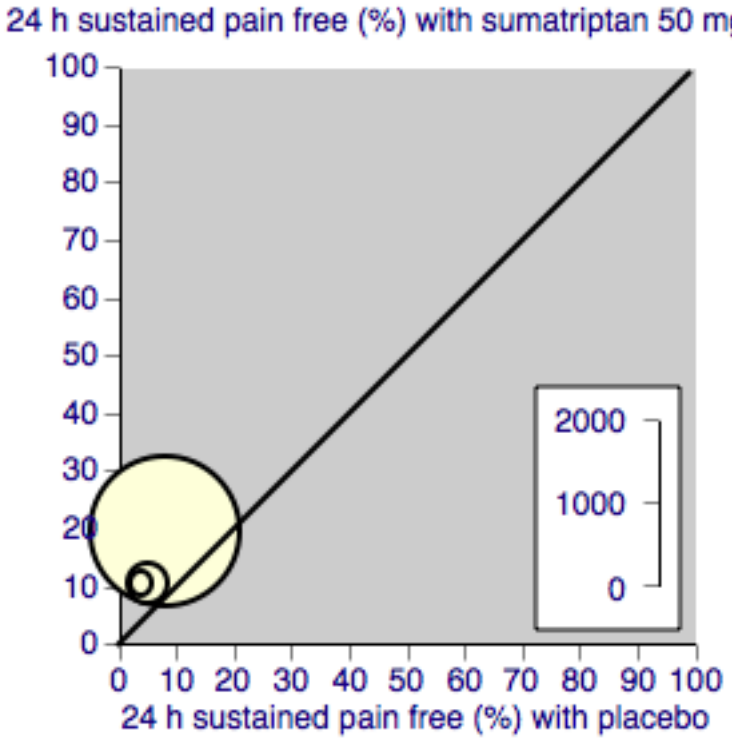


Figure 10. L'Abbé plot showing results for sumatriptan 50 mg versus placebo for sustained pain-free during 24 hours. Each circle represents a different study; size of circle is proportional to size of study; diagonal is line of equivalence



WHAT'S NEW

Date	Event	Description
29 May 2019	Amended	Contact details updated.
1 May 2015	Review declared as stable	A search for studies is likely to identify potentially relevant studies, but the studies are unlikely to change conclusions.

CONTRIBUTIONS OF AUTHORS

SD and RAM wrote the protocol. CD and SD carried out searches, data extraction, and analyses. RAM acted as arbitrator. All authors were involved with writing the final review.

DECLARATIONS OF INTEREST

RAM and SD have received research support from charities, government, and industry sources at various times. RAM has consulted for various pharmaceutical companies, including GlaxoSmithKline, the manufacturers of sumatriptan. RAM has received lecture fees from pharmaceutical companies related to analgesics and other healthcare interventions. CD has no interests to declare. GlaxoSmithKline were not in any way involved in conducting this review.

SOURCES OF SUPPORT

Internal sources

- Oxford Pain Relief Trust, UK.

External sources

- Cochrane Review Incentive Scheme 2010, UK.
- *Lifting The Burden:* the Global Campaign against Headache, UK.

Funding for administrative costs associated with editorial and peer review

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have considered data for three outcomes not specified in the protocol.

- Use of rescue medication was reported by the majority of studies, and provides a measure of efficacy from the point of view of the patient. In taking rescue medication the patient is saying that the efficacy of the medication is not adequate and that they need alternative analgesia. They are effectively withdrawing due to lack of efficacy, where efficacy is defined by their preparedness to carry on without additional analgesia, rather than a predefined outcome such as headache relief at two hours. We believe this is useful additional information relevant to clinical practice.
- Pain-free at one hour provides, along with headache relief at one hour, a measure of the speed of onset of the medication. This is an important feature of some anti-migraine treatments and can vary significantly between different routes of administration of the same drug. We chose to analyse pain-free at one hour to provide a stringent measure of the early efficacy of oral sumatriptan, which we believe to be important information for clinical practice.
- Headache relief over multiple (two or three) attacks was reported in five studies. We chose to analyse this because it provides useful information about whether initial response to medication is maintained in subsequent attacks.

Several studies allowed participants the option of a second dose of study medication under certain conditions and apparently continued to collect adverse event data after this. We performed sensitivity analyses to investigate the possible effect on the incidence of adverse events of including these studies.

We have included data for withdrawals due to adverse events over reporting periods longer than the 24 hours stated in the protocol. Many studies collected adverse event data for longer than 24 hours after treatment, and it is likely that in these cases data on withdrawals due to adverse events were also collected over longer time periods. Adverse event withdrawals were infrequent in all of the trials reporting, regardless of the time period over which they were collected, but are an important measure of drug safety and tolerability. We therefore decided to be as inclusive as possible with data on adverse event withdrawals, in the hope of providing the most comprehensive picture possible of sumatriptan tolerability.

For calculations of susceptibility to publication bias we have used a NNT of ≥ 8 as the limit of clinical utility for pain-free at two hours and ≥ 6 for headache relief at two hours. In the protocol we said we would use a NNT of ≥ 8 for headache relief at two hours, but made the change following a discussion with the field editor.

NOTES

This review is one of a series of reviews on sumatriptan for acute migraine attacks in adults which replaces an earlier Cochrane review of oral sumatriptan (McCrory 2003).

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Administration, Oral; Analgesics [administration & dosage]; Migraine Disorders [*drug therapy]; Randomized Controlled Trials as Topic; Serotonin 5-HT1 Receptor Agonists [*administration & dosage] [adverse effects]; Sumatriptan [*administration & dosage] [adverse effects]; Time Factors; Treatment Outcome

MeSH check words

Adult; Humans