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Triptans for acute cluster headache (Review)

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[Intervention Review]

Triptans for acute cluster headache

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ABSTRACT

Background

This is an updated version of the original Cochrane review published in Issue 4, 2010 ([Law 2010](#)). Cluster headache is an uncommon, severely painful, and disabling condition, with rapid onset. Validated treatment options are limited; first-line therapy includes inhaled oxygen. Other therapies such as intranasal lignocaine and ergotamine are not as commonly used and are less well studied. Triptans are successfully used to treat migraine attacks and they may also be useful for cluster headache.

Objectives

To assess the efficacy and tolerability of the triptan class of drugs compared to placebo and other active interventions in the acute treatment of episodic and chronic cluster headache in adult patients.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, ClinicalTrials.gov, and reference lists for studies from inception to 22 January 2010 for the original review, and from 2009 to 4 April 2013 for this update.

Selection criteria

Randomised, double-blind, placebo-controlled studies of triptans for acute treatment of cluster headache episodes.

Data collection and analysis

Two review authors independently assessed study quality and extracted data. Numbers of participants with different levels of pain relief, requiring rescue medication, and experiencing adverse events and headache-associated symptoms in treatment and control groups were used to calculate relative risk and numbers needed to treat for benefit (NNT) and harm (NNH).

Main results

New searches in 2013 did not identify any relevant new studies.

All six included studies used a single dose of triptan to treat an attack of moderate to severe pain intensity. Subcutaneous sumatriptan was given to 131 participants at a 6 mg dose, and 88 at a 12 mg dose. Oral or intranasal zolmitriptan was given to 231 participants at a 5 mg dose, and 223 at a 10 mg dose. Placebo was given to 326 participants.

Triptans were more effective than placebo for headache relief and pain-free responses. By 15 minutes after treatment with subcutaneous sumatriptan 6 mg, 48% of participants were pain-free and 75% had no pain or mild pain (17% and 32% respectively with placebo). NNTs for subcutaneous sumatriptan 6 mg were 3.3 (95% CI 2.4 to 5.0) and 2.4 (1.9 to 3.2) respectively. Intranasal zolmitriptan 10 mg was of

less benefit, with 12% of participants pain-free and 28% with no or mild pain (3% and 7% respectively with placebo). NNTs for intranasal zolmitriptan 10 mg were 11 (6.4 to 49) and 4.9 (3.3 to 9.2) respectively.

Authors' conclusions

Based on limited data, subcutaneous sumatriptan 6 mg was superior to intranasal zolmitriptan 5 mg or 10 mg for rapid (15 minute) responses, which are important in this condition. Oral routes of administration are not appropriate.

PLAIN LANGUAGE SUMMARY

Triptans for acute cluster headache

Cluster headaches are excruciating headaches of extreme intensity. They can last for several hours, are usually on one side of the head only, and affect men more than women. Multiple headaches can occur over several days. Fast pain relief is important because of the intense nature of the pain with cluster headache.

Triptans are a type of drug used to treat migraine. Although migraine is different from cluster headache, there are reasons to believe that some forms of these drugs could be useful in cluster headache. Triptans can be given by injection under the skin (subcutaneously) or by a spray into the nose (intranasally) to produce fast pain relief.

The review found six studies examining two different triptans. The number of people in the studies was limited. Within 15 minutes of using subcutaneous sumatriptan 6 mg, almost 8 in 10 participants had no worse than mild pain, and 5 in 10 were pain-free. Within 15 minutes of using intranasal zolmitriptan 5 mg, about 3 in 10 had no worse than mild pain, and 1 in 10 was pain-free. Adverse events were more common with a triptan than with placebo but they were generally of mild to moderate severity.

Cluster headache is an awful thing to have. More research on how to get better pain relief faster, and to more patients, would be welcome.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Intranasal zolmitriptan 5 mg compared with placebo for acute cluster headache

Patient or population: adults with cluster headache

Settings: community

Intervention: intranasal zolmitriptan 5 mg

Comparison: placebo

Outcomes	Probable out-come with intervention	Probable out-come with comparator	NNT or NNTH and/or relative effect (95% CI)	No of studies, attacks, events	Quality of the evidence (GRADE)	Comments
Pain-free at 30 mins	320 in 1000	180 in 1000	NNT 6.9 (3.9 to 30)	2 studies, 228 attacks, 58 events	Low	
Pain-free at 15 mins	81 in 1000	32 in 1000	RR 2.6 (0.80 to 8.5)	2 studies, 228 attacks, 12 events	Very low	
Headache relief at 30 mins	450 in 1000	260 in 1000	NNT 6.7 (4.2 to 17)	2 studies, 228 attacks, 82 events	Low	
Headache relief at 15 mins	150 in 1000	70 in 1000	RR 2.2 (0.99 to 4.67)	2 studies, 228 attacks, 26 events	Very low	
At least one AE	250 in 1000	160 in 1000	RR 1.8 (1.2 to 2.8)	1 studies, 102 attacks, 21 events	Very low	
Serious AE	No events within 72 hours of study medication					

CI: Confidence interval; **NNT:** number needed to treat; **RR:** relative risk; **AE:** adverse event

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

Evidence downgraded because of threat from potential publication bias and chance effects with modest effect size and small numbers of events.

Summary of findings 2.

Subcutaneous sumatriptan 6 mg compared with placebo for acute cluster headache

Patient or population: adults with cluster headache

Settings: community

Intervention: subcutaneous sumatriptan 6 mg

Comparison: placebo

Outcomes	Probable outcome with intervention	Probable outcome with comparator	NNT or NNTH and/or relative effect (95% CI)	No of studies, attacks, events	Quality of the evidence (GRADE)	Comments
Pain-free at 30 mins	no data					
Pain-free at 15 mins	480 in 1000	170 in 1000	NNT 3.3 (2.4 to 5.0)	2 studies, 258 attacks, 85 events	Low	
Headache relief at 30 mins	no data					
Headache relief at 15 mins	750 in 1000	320 in 1000	NNT 2.4 (1.9 to 3.2)	2 studies, 258 attacks, 139 events	Low	
At least one AE	340 in 1000	190 in 1000	NNH 6.6 (4.0 to 19)	2 studies, 293 attacks, 78 events	Very low	
Serious AE	No events					

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

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

Evidence downgraded because of threat from potential publication bias and chance effects with modest effect size and small numbers of events.

BACKGROUND

This is an updated version of the original Cochrane review published in Issue 4, 2010 ([Law 2010](#)).

Description of the condition

Cluster headache is a most painful form of primary headache. Diagnosis is clinical with emphasis on pain, periodicity, and autonomic features. The diagnostic criteria of the International Headache Society (IHS), which are used in clinical trials, describe cluster headache as "attacks of severe, strictly unilateral pain which is orbital, supraorbital, temporal or in any combination of these sites, lasting 15 to 180 minutes and occurring from once every other day to eight times per day" and associated with one or more of various ipsilateral symptoms (conjunctival injection, lacrimation, nasal congestion, rhinorrhoea, forehead and facial sweating, miosis, ptosis or eyelid oedema) ([IHS 2004](#); [Appendix 1](#)).

It is important to note some key definitions used in the descriptions of cluster headache. An 'attack' is an individual episode of headache, and a 'cluster period' is a series of such attacks. The major division of cluster headache is between episodic and chronic types. Episodic cluster headache is defined as "cluster headache attacks occurring in periods lasting 7 days to 1 year separated by pain-free periods (remissions) lasting 1 month or longer", while chronic cluster headache is defined as "attacks occurring for more than 1 year without remission or with remissions lasting less than 1 month" ([IHS 2004](#)).

The prevalence of cluster headache is estimated to be 0.02% to 0.4%, with a male preponderance ([D'Alessandro 1986](#); [Tfelt-Hansen 2012](#); [Torelli 2005](#)). Onset is most commonly at between 20 to 40 years of age ([Ekblom 1978](#)). First and second degree relatives of individuals with cluster headache are more likely to suffer themselves (with up to 20-fold and 3-fold increased risk respectively), but the genes involved have not been identified and there is likely to be an interaction between genes and environmental factors (for example smoking, alcohol, head trauma) ([Russell 2004](#); [Sjöstrand 2010](#)). In some individuals attacks can be triggered by factors such as alcohol, perfume or paint, or sleep ([Nesbitt 2012](#)). Cluster headache pain has a rapid onset and lasts from 15 minutes to 3 hours.

Treatment for cluster headache attacks can be either preventative or acute. Preventative treatment aims to decrease the incidence of attacks; acute therapy is directed at alleviating the symptoms of an individual attack when it occurs. This review looked at acute therapies only. Given the severity, rapid onset, and short time to peak intensity, treatment has to be swift and effective. Validated treatment options are limited; first-line therapy includes inhaled oxygen, although a recent survey in the United States indicates that this is under- and poorly utilised ([Rozen 2011](#)). Alternative therapies such as intranasal lignocaine and ergotamine are not as commonly used and are less well studied.

Description of the intervention

Triptans are selective agonists at the ligand gated, G-protein linked serotonergic, or 5-hydroxytryptamine (5-HT, or serotonin) receptors. Several drugs within the 'triptan' class are licensed for use in primary headache. These drugs have been extensively studied for the acute treatment of migraine. Because cluster headache shares some clinical features with migraine, triptans have also

been studied for the acute treatment of cluster headache using the oral and the more rapid intranasal or subcutaneous routes of administration ([Plosker 1994](#)).

How the intervention might work

There is no current unifying theory to explain cluster headaches. Positron emission tomography (PET) has been used to look at regional cerebral changes in blood flow during acute attacks. From these imaging studies it appears that areas in the brain stem, such as the hypothalamus, may act as a neurological origin for cluster headache ([May 1998](#)). Alcohol, nitrates, and carbon dioxide are known to precipitate cluster headache. Similar inflammatory metabolic intermediaries such as calcitonin gene related peptide (CGRP), substance P, somatostatin, and histamine, all with vasodilatory properties, are also known to provoke attacks ([Cluster Headache Study Group 1991](#)). Despite this, such evidence does not fully answer why cluster headaches have circadian rhythmicity, are unilateral, and have a male preponderance.

Cluster headaches are therefore thought to be a neurovascular phenomenon with contributions from central and peripheral mechanisms. The hypothalamus, or a closely related structure, is involved as a candidate site of origin. This could cause severe unilateral pain by activation of the trigeminal nerve complex with autonomic symptoms as a result of perivascular activation and increased cranial parasympathetic outflow.

Serotonergic receptors are distributed ubiquitously around the brain stem and trigeminal complex. Agonism of these receptors by the triptan class of drugs is thought to be responsible for their therapeutic effect. This effect could be mediated by inhibition of trigeminal nerve endings in large cerebral vessels, direct vasoconstriction of these associated vessels, and neuronal inhibition of more central hypothalamic lesions.

Route of administration may of particular importance in cluster headache because of the need for rapid relief. The subcutaneous route might be expected to provide the best results since there is rapid absorption, followed by the intranasal or sublingual routes (where absorption may be partly enteral and partly parenteral), with oral tablets likely to be least rapid due to slower absorption. In practice this may limit the choice of triptan for cluster headache, since only sumatriptan is available as a subcutaneous formulation, only zolmitriptan as a nasal spray, and only rizatriptan as a melt wafer. All are available as oral tablets.

Why it is important to do this review

Although cluster headache affects a relatively small proportion of people, it is an extremely painful and disabling condition. At the time of the original review there was no systematic review of the evidence for the efficacy and tolerability of the triptan class of drugs for acute cluster headache. The review filled that gap using methods that allowed comparison between individual drugs and routes of administration in standardised trials.

In the three years since then, there have been improvements in the way we assess and report evidence in Cochrane reviews. It was felt important to see if any further studies have been carried out since the original review and to update the review in line with current standards.

OBJECTIVES

To assess the efficacy and tolerability of the triptan class of drugs compared to placebo and other active interventions in the acute treatment of episodic and chronic cluster headache in adult patients.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised, double-blind, placebo-controlled or active-controlled studies using a triptan to treat a discrete cluster headache episode, with a minimum of 10 participants per treatment arm. We accepted studies reporting treatment of consecutive headache episodes if outcomes for the first, or each, episode were reported separately; we used first-attack data preferentially. We accepted cross-over studies if there was adequate (preferably ≥ 24 hours) washout between treatments.

Types of participants

Studies included adults (at least 18 years of age) with cluster headache. We used the definition of cluster headache specified by the International Headache Society (IHS) (IHS 1988 or IHS 2004), although other definitions were considered if they conformed in general to IHS diagnostic criteria. There were no restrictions on cluster headache frequency, duration, or type (episodic or chronic). We accepted studies including participants taking stable prophylactic therapy to reduce headache frequency; details on the prophylactic therapy prescribed or allowed are provided in the [Characteristics of included studies](#) table.

Types of interventions

We included studies that used a single dose of any triptan to treat a cluster headache episode when pain was of moderate to severe intensity, or that investigated different dosing strategies or timing of the first dose in relation to headache intensity. There was no restriction on dose or route of administration, provided the medication could be self-administered.

A placebo comparator is essential to demonstrate that triptans are effective in this condition, and the main comparison considered was triptan versus placebo. Where studies had both a placebo and active comparator, data were sought for direct comparison of triptan versus the active comparator. Active-controlled trials without a placebo, such as equivalence trials, were considered as secondary evidence if the trial was judged to have validity by accepted criteria (McAlister 2001). We excluded studies designed to demonstrate prophylactic efficacy in reducing the number or frequency of cluster headaches.

Types of outcome measures

Measures of pain intensity or pain relief had to be made by the patient (not the investigator or care giver) using a standard 5-point categorical scale (pain intensity: none, mild, moderate, severe, very severe or excruciating; pain relief: none, a little, some, a lot, complete) or 100 mm visual analogue scale (VAS) (IHS Trial Guidelines 1995; Moore 2003).

Primary outcomes

The primary outcomes considered (see [Differences between protocol and review](#)) were:

- headache relief (assessed on the 5-point pain relief scale described above, or defined as a reduction in pain intensity from moderate or severe or very severe to none or mild) at 15, 30, or 60 minutes, without use of rescue medication;
- pain-free at 15, 30, or 60 minutes, without use of rescue medication.

Secondary outcomes

Secondary outcomes to be considered were:

- time to pain-free response;
- time to headache relief response;
- adverse events: any, serious, withdrawal, reported within 24 hours post-dose.

Other outcomes

- Relief of headache-associated symptoms
- Use of rescue medication
- Recurrence of headache

These are not now reported in detail in 'Results' but have been moved to an Appendix (see [Differences between protocol and review](#)).

Search methods for identification of studies

Electronic searches

We searched the following databases:

- the Cochrane Central Register of Controlled Trials (CENTRAL) (to Issue 1, 2010, for the original review and to Issue 3, 2013, for the update);
- MEDLINE (via Ovid) (from inception to 22 January 2010 for the original review, and 2009 to 4 April 2013 for the update);
- EMBASE (via Ovid) (from inception to 22 January 2010 for the original review, and 2009 to 4 April 2013 for the update).

See [Appendix 2](#) for the search strategy for MEDLINE, [Appendix 3](#) for the search strategy for EMBASE, and [Appendix 4](#) for the search strategy for CENTRAL. There were no language restrictions.

Searching other resources

We searched reference lists of retrieved studies and review articles for additional studies, and [ClinicalTrials.gov](#) on 4 April 2013. Grey literature and abstracts were not searched.

Data collection and analysis

Selection of studies

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

Data extraction and management

Two review authors independently extracted data from included studies using a standard data extraction form. Disagreements were settled by discussion with a third review author. Data were entered into RevMan 5 (RevMan 2012) by one author.

Assessment of risk of bias in included studies

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

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

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

Measures of treatment effect

Dichotomous data

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

We planned to use the following terms to describe adverse outcomes in terms of harm or prevention of harm.

- When significantly fewer adverse outcomes occurred with triptans than with control (placebo or active) we use the term the number needed to treat to prevent one event (NNTp).
- When significantly more adverse outcomes occurred with triptans than with control (placebo or active) we use the term the number needed to harm or cause one event (NNH).

Time-to-event data

We weighted time-to-event data by study size and presented them as the weighted mean of the median or mean.

Unit of analysis issues

The unit of analysis was the individual patient.

Dealing with missing data

The most likely source of missing data was cross-over studies; where possible in such cases we would use only first-period data.

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

Assessment of heterogeneity

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

Assessment of reporting biases

We assessed publication bias by examining the number of participants in trials with zero effect (relative risk of 1.0) needed for the point estimate of the NNT to increase beyond a clinically useful level (Moore 2008). In this case, we calculated numbers needed for NNT cut-offs of 8 and 10.

Data synthesis

We planned to analyse studies using a single dose of a triptan in established pain of at least moderate intensity separately from studies in which medication was taken before pain was well established or in which a second dose of medication was permitted. In fact, no studies were identified that examined early treatment of attacks before pain was of at least moderate intensity. Similarly, none of the included studies employed multiple dosing strategies for a single attack.

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). We assumed a statistically significant difference from control when the 95% CI of the relative benefit did not include the number one.

We determined significant differences between NNT, NNTp, and NNH for different groups in subgroup and sensitivity analyses, using the z test (Tramèr 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

Issues for subgroup analysis were drug, dose, and route of administration.

Sensitivity analysis

We planned sensitivity analysis for study quality (Oxford Quality Score of 2 versus 3 or more), and for headache type (episodic versus chronic cluster headache). A minimum of two studies and 200 participants were required for any sensitivity analysis.

RESULTS

Description of studies

Results of the search

Searching identified eight potentially relevant studies.

Included studies

Six studies satisfied the inclusion criteria (Bahra 2000; Cittadini 2006; Ekbom 1991; Ekbom 1993; Rapoport 2007; Van Vliet 2003) and all were cross-over in design. One of these studies (Van Vliet 2003) treated two headache episodes with each study medication and did not provide data for each episode separately. We decided to include the study, subject to a sensitivity analysis, but since it was the only study using sumatriptan 20 mg, data from it were not pooled; results are presented where appropriate. The remaining five studies treated one headache episode with each study medication. These five studies included washout periods between cross-over periods of 18 to 24 hours. All reported negative tests for period effect, so we combined data from all headaches treated with each medication in our analyses.

All of the included studies used a single dose of a triptan when the headache was of at least moderate intensity; all used a similar five-point scale to assess headache pain intensity. No studies were identified examining early treatment of attacks before pain was of at least moderate intensity. Similarly, no studies employed multiple dosing strategies for a single attack.

All studies were multicentred and diagnosed cluster headache according to IHS criteria. Most required that participants had previously tolerated treatment with a triptan or had no contraindications, or both, but Ekbom 1991 and Ekbom 1993

recruited only sumatriptan-naïve participants. In four studies participants self-treated their headaches at home (Bahra 2000; Cittadini 2006; Rapoport 2007; Van Vliet 2003), while in the other two medication was administered by a physician or nurse in hospital (Ekbom 1991; Ekbom 1993). We included these hospital-based studies because although the intervention was not self-administered in these cases, subcutaneous sumatriptan can be, and is commonly, self-administered.

The mean age of participants ranged from 40 to 44 years, and between 60% to 87% were men. The studies included participants with diagnoses of both episodic and chronic types of cluster headache, with between 56% and 75% having episodic-type headaches. Two studies reported some results for episodic and chronic headaches separately (Bahra 2000; Cittadini 2006). No participants were using prophylactic medication. All studies appeared to have an appropriate washout period between study doses, co-analgesics, or rescue medication.

All studies compared a triptan with placebo. No study directly compared one drug with another. Oral zolmitriptan 5 mg and 10 mg were tested in one study (Bahra 2000), and intranasal zolmitriptan 5 mg and 10 mg in two studies (Cittadini 2006; Rapoport 2007). Subcutaneous sumatriptan 6 mg was tested in two studies (Ekbom 1991; Ekbom 1993), subcutaneous sumatriptan 12 mg in one (Ekbom 1993), and intranasal sumatriptan 20 mg in one study (Van Vliet 2003). In total, 231 participants received zolmitriptan 5 mg, 223 received zolmitriptan 10 mg, 131 received sumatriptan 6 mg, 88 received sumatriptan 12 mg, 77 received sumatriptan 20 mg, and 430 received placebo.

The outcomes reported by individual studies are listed in the [Characteristics of included studies](#) table. Most studies evaluated headache relief and pain-free response at 30 minutes as the primary outcome measures. Two of the six studies evaluated headache relief and pain-free response as the primary outcome measures at an earlier time of 15 minutes (Ekbom 1991; Ekbom 1993). One study (Rapoport 2007) reported these outcomes at various time points up to 60 minutes. Dichotomous data on the use of rescue medication were reported for all trials. Two studies did not report numerical data on adverse events (Cittadini 2006; Van Vliet 2003). All studies except Rapoport 2007 reported data on relief of associated symptoms, but not in a consistent way. No data were presented on headache recurrence. Only one study reported data on time to a response: initial headache relief (Van Vliet 2003).

Details are provided in the [Characteristics of included studies](#) table.

Excluded studies

Two publications describing three trials were excluded (Goadsby 1994; Hardebo 1998). Details are provided in the '[Characteristics of excluded studies](#)' table.

Risk of bias in included studies

Methodological quality, assessed using the Oxford Quality Scale, was good in all studies. Three studies scored 5/5 (Bahra 2000; Ekbom 1991; Rapoport 2007), and three scored 4/5 (Cittadini 2006; Ekbom 1993; Van Vliet 2003). Points were lost due to failure to adequately report the method of randomisation or blinding. All studies reported withdrawals and dropouts. Full details are provided in the '[Characteristics of included studies](#)' table.

In addition, a 'Risk of bias' table was created, which considered sequence generation, allocation concealment, blinding, incomplete outcome data, and study size (Figure 1). Only two studies adequately reported the method of allocation

concealment (Cittadini 2006; Rapoport 2007), and two studies (Ekblom 1991; Rapoport 2007) were considered at high risk of bias due to small numbers of treated attacks. No study had substantial amounts of missing data without a valid reason.

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

Effects of interventions

See: [Summary of findings for the main comparison; Summary of findings 2](#)

Details of selected efficacy outcomes for individual studies are provided in [Appendix 5](#).

Primary outcomes (Summary of results A)

For the primary outcomes of interest, we focused on results from 15 and 30 minutes post-treatment. The limited data available from 60 minutes are described in the text for completeness, but are not included in the summary tables or analyses (see [Differences between protocol and review](#)).

Pain-free at 15 minutes

Zolmitriptan

Two studies using the intranasal formulation provided data (Cittadini 2006; Rapoport 2007). Both tested 5 mg and 10 mg doses; 117 participants were treated with zolmitriptan 5 mg, 112 with zolmitriptan 10 mg, and 111 with placebo.

Zolmitriptan (nasal spray) 5 mg versus placebo

- The proportion of attacks pain-free at 15 minutes with zolmitriptan 5 mg was 8% (9/117; range 2% to 15%).
- The proportion of attacks pain-free at 15 minutes with placebo was 3% (3/111; range 0% to 6%).
- The relative benefit of treatment compared with placebo was 2.6 (95% CI 0.80 to 8.5) (Analysis 1.1; Figure 2). The NNT was not calculated.

Figure 2. Forest plot of comparison: 1 Zolmitriptan 5 mg versus placebo, outcome: 1.1 Participants pain-free at 15 minutes.

Zolmitriptan (nasal spray) 10 mg versus placebo

- The proportion of attacks pain-free at 15 minutes with zolmitriptan 10 mg was 12% (13/112; range 3% to 22%).
- The proportion of attacks pain-free at 15 minutes with placebo was 3% (3/111; range 0% to 6%).
- The relative benefit of treatment compared with placebo was 3.9 (1.3 to 12) ([Analysis 2.1](#)); the NNT for pain-free response at 30 minutes was 11 (6.4 to 49).

Sumatriptan

Sumatriptan (subcutaneous) 6 mg versus placebo

Two studies using subcutaneous sumatriptan 6 mg provided data ([Ekblom 1991](#); [Ekblom 1993](#)); 131 participants were treated with sumatriptan and 127 with placebo.

- The proportion of attacks pain-free at 15 minutes with sumatriptan 6 mg was 48% (63/131; range 46% to 49%).
- The proportion of attacks pain-free at 15 minutes with placebo was 17% (22/127; range 10% to 20%).
- The relative benefit of treatment compared with placebo was 2.8 (1.8 to 4.2) ([Figure 3](#)); the NNT for pain-free at 15 minutes was 3.3 (2.4 to 5.0).

Figure 3. Forest plot of comparison: 4 Sumatriptan 6 mg versus placebo, outcome: 4.2 Participants pain-free at 15 minutes.

Sumatriptan (subcutaneous) 12 mg versus placebo

One study compared subcutaneous sumatriptan 12 mg with placebo ([Ekblom 1993](#)); 53/88 attacks treated with sumatriptan and 18/88 treated with placebo achieved this outcome ([Appendix 5](#)). There were insufficient data for analysis.

Comparing results for intranasal zolmitriptan 10 mg with subcutaneous sumatriptan 6 mg gave Z = 3.38, P < 0.0008, indicating superiority of subcutaneous sumatriptan.

Pain-free at 30 minutes

Zolmitriptan

Two studies using the intranasal formulation provided data ([Cittadini 2006](#); [Rapoport 2007](#)). Both tested 5 mg and 10 mg doses; 117 participants were treated with zolmitriptan 5 mg, 112 with zolmitriptan 10 mg, and 111 with placebo.

Zolmitriptan (nasal spray) 5 mg versus placebo

- The proportion of attacks pain-free at 30 minutes with zolmitriptan 5 mg was 32% (38/117; range 28% to 38%).
- The proportion of attacks pain-free at 30 minutes with placebo was 18% (20/111; range 16% to 20%).
- The relative benefit of treatment compared with placebo was 1.8 (1.1 to 2.9) ([Analysis 1.2](#)); the NNT for pain-free response at 30 minutes was 6.9 (3.9 to 30).

Zolmitriptan (nasal spray) 10 mg versus placebo

- The proportion of attacks pain-free at 30 minutes with zolmitriptan 10 mg was 48% (54/112; range 47% to 49%).

- The proportion of attacks pain-free at 30 minutes with placebo was 18% (20/111; range 16% to 20%).
- The relative benefit of treatment compared with placebo was 2.7 (1.7 to 4.2) ([Analysis 2.2](#)); the NNT for pain-free response at 30 minutes was 3.3 (2.4 to 5.4).

Zolmitriptan (nasal spray) 10 mg versus 5 mg

The two studies using intranasal zolmitriptan 5 mg and 10 mg provided sufficient data for direct comparison of the two doses for this outcome.

- The proportion of attacks pain-free at 30 minutes with zolmitriptan 10 mg was 48% (54/112; range 47% to 49%).
- The proportion of attacks pain-free at 30 minutes with zolmitriptan 5 mg was 32% (38/117; range 28% to 38%).
- The relative benefit of 10 mg compared with 5 mg was 1.5 (1.1 to 2.1) ([Analysis 3.1](#)); the NNT for pain-free response at 30 minutes for 10 mg compared to 5 mg was 6.4 (3.5 to 32).

Sumatriptan

One study, using intranasal sumatriptan 20 mg, reported this outcome ([Van Vliet 2003](#)); 36/77 attacks treated with sumatriptan, and 14/77 treated with placebo achieved this outcome ([Appendix 5](#)). There were insufficient data for analysis.

Headache relief at 15 minutes

Zolmitriptan

Two studies using the intranasal formulation provided data ([Cittadini 2006](#); [Rapoport 2007](#)). Both tested 5 mg and 10 mg doses;

117 participants were treated with zolmitriptan 5 mg, 112 with zolmitriptan 10 mg, and 111 with placebo.

Zolmitriptan (nasal spray) 5 mg versus placebo

- The proportion of attacks with headache relief at 15 minutes with zolmitriptan 5 mg was 15% (18/117; range 9% to 23%).
- The proportion of attacks with headache relief at 15 minutes with placebo was 7% (8/111; range 2% to 14%).
- The relative benefit of treatment compared with placebo was 2.2 (0.99 to 4.7) (Analysis 1.3). The NNT was not calculated.

Zolmitriptan (nasal spray) 10 mg versus placebo

- The proportion of attacks with headache relief at 15 minutes with zolmitriptan 10 mg was 28% (31/112; range 19% to 39%).
- The proportion of attacks with headache relief at 15 minutes with placebo was 7% (8/111; range 2% to 14%).

- The relative benefit of treatment compared with placebo was 3.9 (1.9 to 8.0) (Analysis 2.3); the NNT for headache relief at 15 minutes was 4.9 (3.3 to 9.2).

Sumatriptan

Sumatriptan (subcutaneous) 6 mg versus placebo

Two studies using subcutaneous sumatriptan provided data (Ekblom 1991; Ekblom 1993); 131 participants were treated with sumatriptan and 127 with placebo.

- The proportion of attacks with headache relief at 15 minutes with sumatriptan 6 mg was 75% (98/131; range 74% to 75%).
- The proportion of attacks with headache relief at 15 minutes with placebo was 32% (41/127; range 26% to 35%).
- The relative benefit of treatment compared with placebo was 2.3 (1.8 to 3.0) (Figure 4); the NNT for headache relief at 15 minutes was 2.3 (1.9 to 3.2).

Figure 4. Forest plot of comparison: 4 Sumatriptan 6 mg versus placebo, outcome: 4.2 Participants with headache relief at 15 minutes.

Sumatriptan (subcutaneous) 12 mg versus placebo

One study compared subcutaneous sumatriptan 12 mg with placebo (Ekblom 1993); 70/88 attacks treated with sumatriptan and 31/88 treated with placebo achieved this outcome. There were insufficient data for analysis.

Comparing results for intranasal zolmitriptan 10 mg with subcutaneous sumatriptan 6 mg gave Z = 2.96, P = 0.003, indicating superiority of subcutaneous sumatriptan.

Headache relief at 30 minutes

Zolmitriptan

Three studies provided data. One (Bahra 2000) used an oral, and two (Cittadini 2006; Rapoport 2007) used an intranasal formulation. All tested both 5 mg and 10 mg doses.

Zolmitriptan (nasal spray) 5 mg versus placebo

- The proportion of attacks with headache relief at 30 minutes with zolmitriptan 5 mg was 45% (53/117; range 42% to 50%).
- The proportion of attacks with headache relief at 30 minutes with placebo was 26% (29/111; range 23% to 30%).
- The relative benefit of treatment compared with placebo was 1.7 (1.2 to 2.5); the NNT for headache relief at 30 minutes was 5.2 (3.2 to 14) (Analysis 1.4).

For the study using the oral formulation only, 62/114 participants (54%) experienced headache relief at 30 minutes compared with 79/226 (43%) with placebo. There were insufficient data for analysis.

Zolmitriptan (nasal spray) 10 mg versus placebo

- The proportion of attacks with headache relief at 30 minutes with zolmitriptan 10 mg was 62% (69/112; range 60% to 63%).
- The proportion of attacks with headache relief at 30 minutes with placebo was 26% (29/111; range 23% to 30%).
- The relative benefit of treatment compared with placebo was 2.4 (1.7 to 3.3); the NNT for headache relief at 30 minutes was 2.8 (2.1 to 4.3) (Analysis 2.4).

For the study using the oral formulation only, 59/111 participants (53%) experienced headache relief at 30 minutes compared with 79/226 (43%) with placebo. There were insufficient data for analysis.

Zolmitriptan (nasal spray) 10 mg versus 5 mg

The two studies using intranasal zolmitriptan 5 mg and 10 mg provided sufficient data for direct comparison of the two doses.

- The proportion of attacks with headache relief at 30 minutes with zolmitriptan 10 mg was 62% (69/112; range 60% to 63%).

- The proportion of attacks with headache relief at 30 minutes with zolmitriptan 5 mg was 45% (53/117; range 42% to 50%).
- The relative benefit of 10 mg compared with 5 mg was 1.4 (1.1 to 1.7); the NNT for headache relief at 30 minutes for 10 mg compared with 5 mg was 6.1 (3.4 to 28) ([Analysis 3.2](#)).

When the study using the oral formulation was included in the analysis, the difference between the 10 mg and 5 mg doses failed to reach the 5% level of significance (RR 1.2 (0.97 to 1.4)).

Sumatriptan

Only one study, using intranasal sumatriptan 20 mg, reported this outcome ([Van Vliet 2003](#)); 44/77 attacks treated with sumatriptan and 20/77 treated with placebo achieved headache relief at 30 minutes ([Appendix 5](#)). There were insufficient data for analysis.

Summary of results A: headache relief and pain-free in placebo-controlled studies							
Drug	Dose (mg)	Route	Studies	Attacks	Triptan %	Placebo %	NNT (95% CI)
Pain-free at 15 minutes							
Zolmitriptan	5	Intranasal	2	228	8.1	3.2	Not calculated
Zolmitriptan	10	Intranasal	2	223	12	3.2	11 (6.4 to 49)
Sumatriptan	6	Subcutaneous	2	258	48	17	3.3 (2.4 to 5.0)
Sumatriptan	12	Subcutaneous	1	176	60	20	Not calculated
Pain-free at 30 minutes							
Zolmitriptan	5	Intranasal	2	228	32	18	6.9 (3.9 to 30)
Zolmitriptan	10	Intranasal	2	223	48	18	3.3 (2.4 to 5.4)
Sumatriptan*	20	Intranasal	1	154	47	18	Not calculated
Headache relief at 15 minutes							
Zolmitriptan	5	Intranasal	2	228	15	7	12 (6.1 to 1700)
Zolmitriptan	10	Intranasal	2	223	28	7	4.9 (3.3 to 9.2)
Sumatriptan	6	Subcutaneous	2	258	75	32	2.4 (1.9 to 3.2)
Sumatriptan	12	Subcutaneous	1	176	80	35	Not calculated
Headache relief at 30 minutes							
Zolmitriptan	5	Oral, intranasal	3	457	50	35	6.7 (4.2 to 17)
Zolmitriptan	5	Intranasal	2	228	45	26	5.2 (3.2 to 14)
Zolmitriptan	10	Oral, intranasal	3	449	57	35	4.5 (3.2 to 7.4)
Zolmitriptan	10	Intranasal	2	223	62	26	2.8 (2.1 to 4.3)
*Sumatriptan	20	Intranasal	1	154	57	26	Not calculated

*This study reported the mean of outcomes for two headache episodes.

Sensitivity analysis of the primary outcomes

All studies had scores for methodological quality of $\geq 3/5$, so no sensitivity analysis was carried out for this criterion. There were insufficient data to compare different routes of administration.

Two studies reported data for episodic and chronic headaches separately for the outcome of headache relief at 30 minutes. One (Bahra 2000) used oral zolmitriptan and the other (Cittadini 2006) used intranasal zolmitriptan, both at 5 mg and 10 mg doses. There were insufficient data for analysis, but results suggest there may be a better response in participants with episodic-type headache than with chronic-type headache in these studies.

Secondary outcomes

Time to pain-free or headache relief (zolmitriptan and sumatriptan)

No studies reported data for the median or mean time to predefined pain relief or pain-free outcomes. Van Vliet 2003 reported the mean time to 'initial relief' with sumatriptan as 12.4 ± 6 minutes, and with placebo as 17.6 ± 12 minutes.

Two studies (Cittadini 2006; Rapoport 2007) using intranasal zolmitriptan 5 mg and 10 mg reported numbers of attacks with headache relief and pain-free response at 5, 10, 15, 20, and 30 minutes post-dose. Rapoport also reported results at 60 minutes. Based on these limited data, the 10 mg dose was better than placebo from about 10 minutes, and the 5 mg dose from about 20 minutes. By 60 minutes only the 10 mg dose remained more effective than placebo, presumably because more headaches had resolved spontaneously by that time.

Two studies (Ekbom 1991; Ekbom 1993) using subcutaneous sumatriptan 6 mg and 12 mg reported numbers of attacks with headache relief and pain-free response at 5, 10, and 15 minutes post-dose. At all time points sumatriptan was better than placebo, with no significant difference between the two doses.

Any adverse event (Summary of results B)

Details of adverse events in individual studies are provided in Appendix 6.

Zolmitriptan

Two studies reported the numbers of participants experiencing any adverse event with zolmitriptan. One (Bahra 2000) specified that the duration over which these data were collected was the 24 hours following dosing, while the other did not specify the time period. Bahra 2000 used an oral formulation, and Rapoport 2007 used the intranasal formulation. Both tested 5 mg and 10 mg doses.

Zolmitriptan (oral and nasal spray) 5 mg versus placebo

- The proportion of attacks with one or more adverse events following treatment with zolmitriptan 5 mg was 27% (45/166; range 25% to 28%).
- The proportion of attacks with one or more adverse events following treatment with placebo was 15% (25/165; range 15% to 16%).

- The relative risk of treatment compared with placebo was 1.8 (1.2 to 2.8) (Analysis 1.5); the NNH was 8.4 (4.8 to 31).

Zolmitriptan (oral and nasal spray) 10 mg versus placebo

- The proportion of attacks with one or more adverse events following treatment with zolmitriptan 10 mg was 37% (59/160; range 33% to 39%).
- The proportion of attacks with one or more adverse events following treatment with placebo was 15% (25/165; range 15% to 16%).
- The relative risk of treatment compared with placebo was 2.4 (1.6 to 3.7) (Analysis 2.5); the NNH was 4.6 (3.2 to 8.0).

The NNH was lower (worse) with the higher dose, but the difference was not statistically significant, with wide and overlapping confidence intervals.

Zolmitriptan (oral and nasal spray) 10 mg versus 5 mg

Direct comparison of the 10 mg and 5 mg doses just failed to show a statistically significant difference: 59/160 participants had an adverse event following treatment with zolmitriptan 10 mg and 45/166 with zolmitriptan 5 mg, giving a relative risk of 1.4 (0.99 to 1.9) (Analysis 3.3).

Sumatriptan

Two studies reported the numbers of participants experiencing any adverse event with sumatriptan, but did not specify the time over which the data were collected. Ekbom 1991 used 6 mg subcutaneously, and Ekbom 1993 used 6 mg and 12 mg subcutaneously.

Sumatriptan (subcutaneous) 6 mg versus placebo

- The proportion of attacks with one or more adverse events following treatment with sumatriptan 6 mg was 34% (51/150; range 34% to 35%).
- The proportion of attacks with one or more adverse events following treatment with placebo was 19% (27/143; range 16% to 26%).
- The relative risk of treatment compared with placebo was 1.8 (1.2 to 2.7) (Analysis 4.3); the NNH was 6.6 (4.0 to 19).

Sumatriptan (subcutaneous) 12 mg versus placebo

Following treatment with sumatriptan 12 mg, 42/94 participants (45%) experienced adverse events compared to 15/96 (16%) with placebo. There were insufficient data for analysis.

Sumatriptan (subcutaneous) 12 mg versus 6 mg

There were insufficient data to compare 12 mg and 6 mg directly, although the results are compatible with more adverse events with the higher dose.

Summary of results B: any adverse event in placebo-controlled studies							
Drug	Dose (mg)	Route	Studies	Attacks	Triptan %	Placebo %	NNH (95% CI)
Zolmitriptan	5	Oral, nasal spray	2	331	27	15	8.4 (4.8 to 31)
Zolmitriptan	10	Oral, nasal spray	2	325	37	15	4.6 (3.2 to 8.0)
Sumatriptan	6	Subcutaneous	2	293	34	19	6.6 (4.0 to 19)
Sumatriptan	12	Subcutaneous	1	190	45	16	Not calculated

Severity of adverse events

Most adverse events were mild or moderate in intensity. Where specifically reported, chest symptoms were of mild or moderate intensity, of short duration, and resolved spontaneously. Fourteen severe adverse events occurred with subcutaneous sumatriptan 6 mg and 12 mg (Ekbom 1993). These were mostly localised reactions around the injection site, and none led to withdrawal.

Specific adverse events

Details of specific adverse events were not consistently reported in these single dose studies (Appendix 7). There were too few data for analysis.

Serious adverse events

One study using oral zolmitriptan 10 mg reported a serious adverse event. This was exacerbation of cluster headache, which occurred 58 days after medication and was considered by the investigators to be unrelated to the study medication (Bahra 2000).

Withdrawals

Details of withdrawals and exclusions in individual studies are provided in Appendix 6.

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

Three withdrawals due to adverse events were reported. One was the result of the serious adverse event reported above (Bahra 2000), one participant withdrew because of shortness of breath and rheumatic pain following 5 mg intranasal zolmitriptan (Cittadini 2006), and one participant withdrew after experiencing moderate pressure on the neck following administration of placebo (Ekbom 1993).

Participants who were excluded from analyses after randomisation were mostly due to major protocol violations or end of cluster period (no medication taken, or cross-over not completed), and were generally well reported. Numbers of participants lost to follow-up, or withdrawing due to unspecified reasons, were small and unlikely to influence results.

DISCUSSION

Summary of main results

This review included six studies comparing either zolmitriptan or sumatriptan with placebo for the acute treatment of cluster headache. Studies used different doses of drug and routes of administration. Zolmitriptan, either orally or as a nasal spray, was given for 454 attacks at doses of 5 mg and 10 mg in comparisons with placebo for 302 attacks. Sumatriptan, either subcutaneous or intranasal, was given for 296 attacks at doses of 6 mg, 12 mg, and 20 mg in comparisons with placebo for 204 attacks.

Because cluster headaches are very intense but short-lasting, effective therapy must be rapid. After 15 minutes, subcutaneous sumatriptan 6 mg gave clinically useful NNTs of about 3 when compared with placebo. For intranasal zolmitriptan 5 mg NNTs were > 10 for both outcomes, and for 10 mg the NNT was 5 for headache relief but > 10 for pain-free at 15 minutes. Comparing results for intranasal zolmitriptan 10 mg with subcutaneous

sumatriptan 6 mg for headache relief and pain-free responses at 15 minutes demonstrated superiority of subcutaneous sumatriptan ($P = 0.003$ and $P < 0.0008$ respectively). The available data support the oral route as being the least significant route of administration and favour the parenteral route, with subcutaneously administered sumatriptan being the most effective for acute cluster headache attack.

Adverse events were more common with triptan than placebo, and zolmitriptan tended to affect more participants at higher doses. For every five individuals treated with zolmitriptan 10 mg and every seven treated with sumatriptan 6 mg, at least one would experience an adverse event(s) who would not have done with placebo. Adverse events were generally of mild or moderate severity and rarely led to withdrawal. Participants reported transient local injection site reactions following subcutaneous sumatriptan, some of which were considered severe and could compromise acceptability of that route of administration. Chest symptoms were of mild or moderate intensity, of short duration, and resolved spontaneously.

Details of specific adverse events and relief of associated symptoms were inconsistently reported, preventing any analysis. Single dose studies are underpowered for investigating specific adverse events, and studies of longer duration will be needed to determine the adverse event profiles of triptans in cluster headache. The safety and tolerability of triptans in migraine are, however, well established and likely to be relevant to this condition (Dodick 2004; Tepper 2003; Welch 2000). The same contraindications in patients with ischaemic heart disease, history of myocardial infarction, uncontrolled hypertension, and the elderly will apply.

Additional analyses (Appendix 8) show that rescue medication was used significantly less often with triptan than with placebo. For every seven attacks treated with zolmitriptan 10 mg, one would not need rescue medication that would have done with placebo; and for every seven treated with subcutaneous sumatriptan 6 mg or 12 mg, two would not need rescue medication which would have done with placebo. In addition, headache-associated symptoms were more improved with triptan than placebo, but there were insufficient data for analysis or firm conclusions.

Overall completeness and applicability of evidence

Interpretation of these results is limited by the small number of studies. Only two drugs were tested, both at two doses, and via two routes of administration. There were inadequate numbers of participants and events to draw firm conclusions about any possible differences between individual drugs, different doses or routes of administration of the same drug, or between subgroups within the treated population. Intranasal and, particularly, subcutaneous administration should theoretically be better than oral administration of the same dose because they avoid problems of hepatic first-pass metabolism; both the number of responders and the speed of response may be improved. Only sumatriptan (subcutaneous and intranasal) and zolmitriptan (intranasal) are available in these formulations. In both studies that analysed data separately for episodic and chronic-type headaches, a better response rate was observed for episodic-type, but there were too few participants with chronic-type headaches to draw firm conclusions. This is compatible with the findings of a one-year study in which fewer patients with chronic cluster headache responded with sumatriptan (Gobel 1998).

The triptans in these trials were used in commonly prescribed doses, which may mean that attacks can be treated safely and without toxicity, with clinically useful levels of efficacy. A limitation on effective treatment may be the currently recommended ceiling doses; during a cluster period, it would be quite possible to use or exceed the maximum daily dose over a short period.

Although the amount of data available for assessment of triptans for cluster headache was not large, it was considerably greater than has been found with other treatments, like oxygen therapy. A Cochrane review of oxygen therapy for migraine and cluster headache (Bennett 2008) found weak evidence for the efficacy of normobaric oxygen therapy in treating acute cluster headache based on 19 participants in a double-blind cross-over study comparing oxygen therapy and air, and 50 participants in an open cross-over study comparing oxygen therapy with ergotamine tartrate. In the comparison with air, 9/16 and 1/14 participants experienced at least significant reduction in headache intensity with oxygen and air respectively. A randomised cross-over trial of 109 adults using high flow oxygen (delivered at 12 litres/min) to treat cluster headache demonstrated efficacy of oxygen compared to placebo. Using the primary endpoint of pain relief at 15 minutes, high flow oxygen produced effective pain relief in 78% of participants compared to 20% using placebo, and this result was noted to be statistically significant (Cohen 2009). While these numbers are too small for indirect comparison, results are compatible with those for triptans in this review.

Quality of the evidence

Methodological quality was good, with all studies scoring above the minimum required to minimise bias. IHS criteria were used for diagnosis of cluster headache in all studies, and well-defined, clinically useful outcomes were reported for efficacy. Detailed reporting of data on adverse events and associated symptoms was inconsistent, but this type of data is not well-captured in single dose studies.

Potential biases in the review process

The methods of the review were such as to minimise bias due to the review process itself, but use of data from both phases of cross-over studies may introduce unknown biases (Elbourne 2002). The five studies that provided data for pooling in this review all reported minimum washout periods of 18 to 24 hours between interventions and found no evidence of carry-over effects. While we believe that using these data does not substantially compromise the results, it must remain a possibility.

The main area of concern is the lack of studies and relatively small numbers of attacks available for analysis, despite using data from all phases of the cross-over studies. No more than two studies contributed to any primary outcome for either drug for a given dose and route of administration. Data for subcutaneous sumatriptan were more robust than for intranasal zolmitriptan. We have calculated that the addition of studies with 602 attacks showing no effect for subcutaneous sumatriptan 6 mg would increase the NNT for headache relief at 15 minutes to 8, or 817 would increase it to 10, a value that we feel is probably the limit of clinical utility. For intranasal zolmitriptan 5 mg the NNT for headache relief at 15 minutes is already greater than 10, while for the 10 mg dose only 141 and 232 attacks with no effect would

be needed to increase the NNT to 8 and 10 respectively. For the outcome of pain-free at 15 minutes, 367 and 524 attacks with no effect would increase the NNT to 8 and 10 respectively for subcutaneous sumatriptan 6 mg; for intranasal zolmitriptan at either 5 mg or 10 mg, the NNTs already exceed 10. This emphasises that the data for subcutaneous sumatriptan are more reliable than for intranasal zolmitriptan.

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 or lower event rates should be interpreted with caution. In this review, the amount of data available is on the limit of acceptability.

Agreements and disagreements with other studies or reviews

A review of medical treatments for cluster headache (Tyagi 2009) identified the same studies involving triptans as this review, but did not carry out any meta-analyses, while a meta-analysis of the two included studies of intranasal zolmitriptan (Hedlund 2009) is in agreement with the findings in this review.

AUTHORS' CONCLUSIONS

Implications for practice

Subcutaneous sumatriptan 6 mg provided headache relief and pain-free outcomes within 15 minutes to many patients with cluster headache causing moderate or severe pain. Intranasal zolmitriptan 10 mg was distinguished from placebo but provided pain relief for few patients at early times. The need for fast delivery to deliver rapid relief in this condition effectively rules out oral administration.

Implications for research

The crucial factor in treating cluster headache is rapid delivery of the intervention or medicine. The methodological requirements are measurement of pain relief over a short time period, within 30 minutes, good methodological quality, and adequate size. Subcutaneous sumatriptan almost certainly be the standard active comparator because use of placebo is probably unethical in this severe condition.

Improvements in the formulation of triptans are unlikely to make a substantial difference to their early efficacy, given a history of formulation research over several decades. Studies comparing triptans with alternative therapy, such as inhaled oxygen, might be useful to determine relative benefits and harms. Combining optimum doses of triptan with oxygen, or with fast-acting non-steroidal anti-inflammatory drug (NSAID) formulations (lysine, arginine, or sodium salts) (Derry 2009) might also be a useful line of research.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Bahra 2000

Methods	Participants recruited from neurology departments; 13 international centres; out-patient based R, DB, three-period cross-over; 20 h washout One headache episode treated for each treatment
Participants	IHS diagnosis of cluster headache for at least three months; able to recognise an attack; excluded if taking any other medications to treat or prevent headache N = 153 randomised, 124 took ≥ 1 medication, 123 in efficacy analysis Mean age 44 ± 11 years 86% men Headache type: 73% episodic
Interventions	Zolmitriptan 5 mg, oral, n = 114 Zolmitriptan 10 mg, oral, n = 111 Placebo, n = 115 Patients instructed to take single dose of trial medication within 10 min of onset if headache was of at least moderate intensity Escape medication permitted after 30 min
Outcomes	Primary: Pain relief to mild or none at 30 min on a five-point scale Secondary: Pain-free at 30 min; relief of associated symptoms; adverse events/withdrawals; use of rescue medication
Notes	Results for primary outcome reported for episodic and chronic subgroups Oxford Quality Score: 5 (R2, DB2, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation sequence
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias)	Low risk	Colour-matched placebo tablets. Four tablets taken in appropriate combination of zolmitriptan 2.5 mg and placebo

Triptans for acute cluster headache (Review)

Bahra 2000 (Continued)

All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts described
Size	Unclear risk	50 to 200 attacks per treatment arm

Cittadini 2006

Methods	Participants recruited from five international study centres; out-patient based R, DB, three-period cross-over; 24 h washout One headache episode treated for each treatment
Participants	Established IHS diagnosis of cluster headache N = 92 randomised, 69 took ≥ 1 medication Mean age 40 $\pm$ 10 years 87% men Headache type: 64% episodic
Interventions	Zolmitriptan 5 mg, nasal spray, n = 65 Zolmitriptan 10 mg, nasal spray, n = 63 Placebo, n = 61 Patients instructed to take medication when headache reached moderate intensity Escape medication permitted after 30 min
Outcomes	Primary: Pain relief to mild or none at 30 min on a five-point scale Secondary: Pain-free at 30 min; relief of associated symptoms; adverse events/withdrawals; use of rescue medication
Notes	Results for primary outcome reported for episodic and chronic subgroups Oxford Quality Score: 4 (R1, DB2, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Randomisation schedule provided by sponsor and kept by pharmacies until study completed
Blinding (performance bias and detection bias) All outcomes	Low risk	Matching placebo

Triptans for acute cluster headache (Review)

Cittadini 2006 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropouts described
Size	Unclear risk	50 to 200 attacks per treatment arm

Ekbom 1991

Methods	Participants recruited from 12 neurology departments; in-patient based study R, DB, two-period cross-over; 24 h washout One headache episode treated with each treatment
Participants	Known IHS diagnosis of cluster headache N = 49 randomised, 39 in efficacy analysis Mean age 42 ± 10 years 79% men Headache type: 56% episodic
Interventions	Sumatriptan 6 mg, subcutaneous, n = 39 Placebo, n = 39 Patients received 0.5 mL injection within 10 min of headache episode of at least moderate intensity Rescue medication permitted after 15 min
Outcomes	Primary: Pain relief to mild or none at 15 min on a five-point scale Secondary: Pain relief at 5 and 10 min; pain-free at 10 and 15 min; associated symptoms; overall functional disability; adverse events/withdrawals; use of rescue medication
Notes	Oxford Quality Score: 5 (R2, DB2, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sequence generated with PACT software programme
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Matching ampoules
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data analysed only for participants who treated both attacks (completer analysis) but valid reasons for exclusion given
Size	High risk	< 50 attacks per treatment arm

Triptans for acute cluster headache (Review)

Ekbom 1993

Methods	<p>Participants recruited from 33 international neurology centres; in-patient based study</p> <p>R, DB, three-period cross-over study; 18 h washout</p> <p>One headache episode treated with each of two treatments</p>
Participants	<p>IHS diagnosis of cluster headache</p> <p>N = 157 randomised, 134 in efficacy analysis</p> <p>Mean age 41 ± 9 years</p> <p>87% men</p> <p>Headache type: 72% episodic</p>
Interventions	<p>Sumatriptan 6 mg, subcutaneous, n = 92</p> <p>Sumatriptan 12 mg, subcutaneous, n = 88</p> <p>Placebo, n = 88</p> <p>Patients received 0.5 mL injection within 10 min of headache episode of at least moderate intensity</p> <p>Rescue medication permitted after 15 min</p>
Outcomes	<p>Primary: Pain relief to mild or none at 10 min on a five-point scale</p> <p>Secondary: Headache relief at 5 and 15 min; pain-free at 15 min; associated symptoms; overall functional disability; adverse events/withdrawals; use of rescue medication</p>
Notes	Oxford Quality Score: 4 (R2, DB1, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Generated by computer
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data analysed only for participants who treated both attacks (completer analysis) but valid reasons for exclusion given
Size	Unclear risk	50 to 200 attacks per treatment arm

Rapoport 2007

Methods	Participants recruited from four headache centres in USA; out-patient based
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Triptans for acute cluster headache (Review)

Rapoport 2007 (Continued)

R, DB, three-period cross-over study; 24 h washout

One headache episode treated with each of three treatments

Participants	<p>Established IHS diagnosis of cluster headache</p> <p>N = 83 randomised, 52 in efficacy analysis</p> <p>Mean age 45 ± 11 years</p> <p>60% men</p> <p>Headache type: 71% episodic</p>
Interventions	<p>Zolmitriptan 5 mg, nasal spray, n = 52 attacks</p> <p>Zolmitriptan 10 mg, nasal spray, n = 49 attacks</p> <p>Placebo, n = 50 attacks</p> <p>Patients instructed to take medication when headache reached at least moderate intensity</p> <p>Escape medication permitted after 60 min</p>
Outcomes	<p>Primary: Pain relief to mild or none at 30 min on a five-point scale</p> <p>Secondary: Complete pain relief (pain-free) at 30 min; headache relief and pain-free at 5, 10, 15, 20, and 60 min; use of rescue medication; adverse events/withdrawals</p>
Notes	Oxford Quality Score: 5 (R2, DB2, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number generation programme
Allocation concealment (selection bias)	Low risk	Individual who generated sequence was blinded to other procedures. Schedules kept by study centre pharmacies until study completion
Blinding (performance bias and detection bias) All outcomes	Low risk	Matching placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts described
Size	High risk	< 50 attacks per treatment arm

Van Vliet 2003

Methods	<p>Participants recruited from five international headache centres; out-patient based</p> <p>R, DB, two-period cross-over study; 24 h washout</p> <p>Two headache episodes treated with each of two treatments</p>
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Triptans for acute cluster headache (Review)

Van Vliet 2003 (Continued)

Participants	<p>Established IHS diagnosis of cluster headache</p> <p>N = 118 randomised, 85 in efficacy analysis</p> <p>Mean age 43 ± 11 years</p> <p>82% men</p> <p>Headache type: 75% episodic</p>
Interventions	<p>Sumatriptan 20 mg, nasal spray, n = 77</p> <p>Placebo, n = 77</p> <p>Patients instructed to take medication when headache reached at least moderate intensity</p> <p>Escape medication permitted after 30 min</p>
Outcomes	<p>Primary: Pain relief to mild or none at 30 min on a five-point scale</p> <p>Secondary: Pain-free at 30 min; relief of associated symptoms; time to initial relief; use of rescue medication; adverse events; withdrawals</p>
Notes	Oxford Quality Score: 4 (R1, DB2, W1)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Matching placebo
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	> 10% dropout rate, but valid reasons for exclusion given
Size	Unclear risk	50 to 200 attacks per treatment arm

Abbreviations: DB - double-blind; N - number of participants in study; n - number of participants in treatment group; R - randomised; W - withdrawals

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Goadsby 1994	Not original research. Uses in its analysis the data from Ekbom 1991 and Ekbom 1993
Hardebo 1998	Open study, not double-blinded

DATA AND ANALYSES

Comparison 1. Zolmitriptan 5 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants pain-free at 15 minutes	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Nasal spray	2	228	Risk Ratio (M-H, Fixed, 95% CI)	2.60 [0.80, 8.46]
2 Participants pain-free at 30 minutes	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Nasal spray	2	228	Risk Ratio (M-H, Fixed, 95% CI)	1.81 [1.12, 2.90]
3 Participants with headache relief at 15 minutes	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Nasal spray	2	228	Risk Ratio (M-H, Fixed, 95% CI)	2.15 [0.99, 4.67]
4 Participants with headache relief at 30 minutes	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Oral	1	229	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.96, 1.63]
4.2 Nasal spray	2	228	Risk Ratio (M-H, Fixed, 95% CI)	1.74 [1.20, 2.51]
5 Participants with any adverse event	2	331	Risk Ratio (M-H, Fixed, 95% CI)	1.79 [1.15, 2.77]
6 Participants using rescue medication	3	457	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.55, 0.91]
6.1 after 30 minutes	2	355	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.52, 0.90]
6.2 after 60 minutes	1	102	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.47, 1.39]

Analysis 1.1. Comparison 1 Zolmitriptan 5 mg versus placebo, Outcome 1 Participants pain-free at 15 minutes.

Analysis 1.2. Comparison 1 Zolmitriptan 5 mg versus placebo, Outcome 2 Participants pain-free at 30 minutes.

Analysis 1.3. Comparison 1 Zolmitriptan 5 mg versus placebo, Outcome 3 Participants with headache relief at 15 minutes.

Analysis 1.4. Comparison 1 Zolmitriptan 5 mg versus placebo, Outcome 4 Participants with headache relief at 30 minutes.

Analysis 1.5. Comparison 1 Zolmitriptan 5 mg versus placebo, Outcome 5 Participants with any adverse event.

Analysis 1.6. Comparison 1 Zolmitriptan 5 mg versus placebo, Outcome 6 Participants using rescue medication.

Comparison 2. Zolmitriptan 10 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants pain-free at 15 minutes	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Nasal spray	2	223	Risk Ratio (M-H, Fixed, 95% CI)	3.90 [1.26, 12.05]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Participants pain-free at 30 minutes	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Nasal spray	2	223	Risk Ratio (M-H, Fixed, 95% CI)	2.68 [1.72, 4.17]
3 Participants with headache relief at 15 minutes	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Nasal spray	2	223	Risk Ratio (M-H, Fixed, 95% CI)	3.90 [1.90, 8.01]
4 Participants with headache relief at 30 minutes	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Oral	1	226	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.93, 1.60]
4.2 Nasal spray	2	223	Risk Ratio (M-H, Fixed, 95% CI)	2.36 [1.67, 3.34]
5 Participants with any adverse event	2	325	Risk Ratio (M-H, Fixed, 95% CI)	2.43 [1.61, 3.68]
6 Participants using rescue medication	3	449	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.50, 0.85]
6.1 after 30 minutes	2	350	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.46, 0.84]
6.2 after 60 minutes	1	99	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.43, 1.33]

Analysis 2.1. Comparison 2 Zolmitriptan 10 mg versus placebo, Outcome 1 Participants pain-free at 15 minutes.

Analysis 2.2. Comparison 2 Zolmitriptan 10 mg versus placebo, Outcome 2 Participants pain-free at 30 minutes.

Analysis 2.3. Comparison 2 Zolmitriptan 10 mg versus placebo, Outcome 3 Participants with headache relief at 15 minutes.

Analysis 2.4. Comparison 2 Zolmitriptan 10 mg versus placebo, Outcome 4 Participants with headache relief at 30 minutes.

Analysis 2.5. Comparison 2 Zolmitriptan 10 mg versus placebo, Outcome 5 Participants with any adverse event.

Analysis 2.6. Comparison 2 Zolmitriptan 10 mg versus placebo, Outcome 6 Participants using rescue medication.

Comparison 3. Zolmitriptan 10 mg versus 5 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants pain-free at 30 minutes	2	229	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [1.07, 2.06]
2 Participants with headache relief at 30 minutes	3	454	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.97, 1.37]
2.1 Oral	1	225	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.77, 1.25]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 Nasal spray	2	229	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [1.06, 1.74]
3 Participants with any adverse event	2	326	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [0.99, 1.87]

Analysis 3.1. Comparison 3 Zolmitriptan 10 mg versus 5 mg, Outcome 1 Participants pain-free at 30 minutes.

Analysis 3.2. Comparison 3 Zolmitriptan 10 mg versus 5 mg, Outcome 2 Participants with headache relief at 30 minutes.

Analysis 3.3. Comparison 3 Zolmitriptan 10 mg versus 5 mg, Outcome 3 Participants with any adverse event.

Comparison 4. Sumatriptan versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants pain-free at 15 minutes	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Subcutaneous 6 mg	2	258	Risk Ratio (M-H, Fixed, 95% CI)	2.77 [1.82, 4.21]
2 Participants with headache relief at 15 minutes	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Subcutaneous 6 mg	2	258	Risk Ratio (M-H, Fixed, 95% CI)	2.31 [1.77, 3.03]
3 Participants with any adverse event	2	293	Risk Ratio (M-H, Fixed, 95% CI)	1.80 [1.20, 2.70]
3.1 Subcutaneous 6 mg	2	293	Risk Ratio (M-H, Fixed, 95% CI)	1.80 [1.20, 2.70]
4 Participants using rescue medication	2	346	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.20, 0.47]
4.1 Subcutaneous 6 mg	2	214	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.19, 0.53]
4.2 Subcutaneous 12 mg	1	132	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.14, 0.58]

Analysis 4.1. Comparison 4 Sumatriptan versus placebo, Outcome 1 Participants pain-free at 15 minutes.

Analysis 4.2. Comparison 4 Sumatriptan versus placebo, Outcome 2 Participants with headache relief at 15 minutes.

Analysis 4.3. Comparison 4 Sumatriptan versus placebo, Outcome 3 Participants with any adverse event.

Analysis 4.4. Comparison 4 Sumatriptan versus placebo, Outcome 4 Participants using rescue medication.

APPENDICES

Appendix 1. International Headache Society criteria for diagnosis of cluster headache

A. At least 5 attacks fulfilling criteria B-D.

B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15-180 minutes if untreated.

C. Headache is accompanied by at least one of the following:

- ipsilateral conjunctival injection and/or lacrimation
- ipsilateral nasal congestion and/or rhinorrhoea
- ipsilateral eyelid oedema
- ipsilateral forehead and facial sweating
- ipsilateral miosis and/or ptosis
- a sense of restlessness or agitation

D. Attacks have a frequency from one every other day to 8 per day.

E. Not attributed to another disorder.

Appendix 2. Search strategy for MEDLINE (via Ovid)

- exp Cluster Headache/
- ((cluster adj4 headache*) or (ciliary adj4 neuralgi*) or (neuralgi* adj4 migraine*) or (histamin* adj4 cephalgi*) or (horton* adj2 syndrome*)).mp.
- 1 or 2
- exp Tryptamines/
- (triptan* or tryptamin*).mp.
- (almotriptan or eletriptan or frovatriptan or naratriptan or rizatriptan or sumatriptan or zolmitriptan).mp.
- or/4-6
- randomized controlled trial.pt.
- controlled clinical trial.pt.
- randomized.ab.
- placebo.ab.
- drug therapy.fs.

- 13.randomly.ab.
- 14.trial.ab.
- 15.groups.ab.
- 16.or/8-15
- 17.Animals.sh. not (humans.sh. and animals.sh.)
- 18.16 not 17
- 19.3 and 7 and 18

Appendix 3. Search strategy for EMBASE (via Ovid)

1. exp Cluster Headache/
2. ((cluster adj4 headache*) or (ciliary adj4 neuralgi*) or (neuralgi* adj4 migraine*) or (histamin* adj4 cephalgi*) or (horton* adj2 syndrome*)).mp.
3. 1 or 2
4. (exp Tryptamines/) or (exp triptans derivative/)
5. (triptan* or tryptamin*).mp.
6. (almotriptan or eletriptan or frovatriptan or naratriptan or rizatriptan or sumatriptan or zolmitriptan).mp.
7. or/4-6
8. clinical trials.sh.
9. controlled clinical trials.sh.
- 10.randomized controlled trial.sh.
- 11.double-blind procedure.sh.
- 12.(clin* adj25 trial*)
- 13.((doubl* or trebl* or tripl*) adj25 (blind* or mask*))
- 14.placebo*
- 15.random*
- 16.or/8-15

Appendix 4. Search strategy for CENTRAL (via Ovid)

1. exp MeSH descriptor Cluster Headache
2. ((cluster adj4 headache*) or (ciliary adj4 neuralgi*) or (neuralgi* adj4 migraine*) or (histamin* adj4 cephalgi*) or (horton* adj2 syndrome*)):ti,ab,kw
3. 1 or 2
4. exp MeSH descriptor Tryptamines
5. (triptan* or tryptamin*):ti,ab,kw
6. (almotriptan or eletriptan or frovatriptan or naratriptan or rizatriptan or sumatriptan or zolmitriptan):ti,ab,kw
7. or/4-6
8. Randomized controlled trial:pt
9. MeSH descriptor Double-blind Method
- 10.random*:ti,ab,kw.
- 11.or 8-10
- 12.3 and 7 and 11
- 13.Limit 12 to Clinical Trials (CENTRAL)

Appendix 5. Summary of outcomes: efficacy and use of rescue medication

Study ID	Treatment	HR 30	PF 30	HR 15	PF 15	Headache re- currence	Use of rescue medica- tion
Bahra 2000	(1) Zolmitriptan 5 mg oral, n = 114 (2) Zolmitriptan 10 mg oral, n = 111 (3) Placebo, n = 115	(1) 62/114 (2) 59/111 (3) 50/115 Episodic; chronic (1) 47/83; 15/31 (2) 47/79; 12/32 (3) 35/83; 15/32	No data	No data	No data	No data	After 30 min: (1) 30/114 (2) 30/111 (3) 46/115 Episodic; chronic (1) 18/83; 12/31 (2) 18/79; 12/32 (3) 37/83; 9/32 Up to 180 min
Cittadini 2006	(1) Zolmitriptan 5 mg IN, n = 65 (2) Zolmitriptan 10 mg IN, n = 63 (3) Placebo, n = 61	(1) 27/65 (2) 38/63 (3) 14/61 Episodic; chronic (1) 17/36; 10/28 (2) 28/35; 8/29 (3) 10/33; 4/28	(1) 18/65 (2) 31/63 (3) 10/61	(1) 6/65 (2) 12/63 (3) 1/61	(1) 1/65 (2) 2/63 (3) 0/61	No data	After 30 min: (1) 23/65 (2) 17/63 (3) 30/61
Ekbom 1991	(1) Sumatriptan 6 mg SC, n = 39 (2) Placebo, n = 39 Not self-administered (physi- cian/nurse)	No data	No data	(1) 29/39 (2) 10/39	(1) 18/39 (2) 4/39	No data	After 15 min: (1) 5/39 (2) 19/39
Ekbom 1993	(1) Sumatriptan 6 mg SC, n = 92 (2) Sumatriptan 12 mg SC, n = 88 (3) Placebo, n = 88 Not self-administered (physi- cian/nurse)	No data	No data	(1) 69/92 (2) 70/88 (3) 31/88	(1) 45/92 (2) 53/88 (3) 18/88	No data	After 15 min: (1) 13/92 (2) 9/88 (3) 33/88
Rapoport 2007	(1) Zolmitriptan 5 mg IN, n = 52 (2) Zolmitriptan 10 mg IN, n = 49 (3) Placebo, n = 50	(1) 26/52 (2) 31/49 (3) 15/50	(1) 20/52 (2) 23/49 (3) 10/50	(1) 12/52 (2) 19/49 (3) 7/50	(1) 8/52 (2) 11/49 (3) 3/50	No data	After 60 min: (1) 16/52 (2) 14/49 (3) 19/50
Van Vliet 2003	(1) Sumatriptan 20 mg IN, n = 77	(1) 44/77	(1) 36/77	No data	No data	No data	After 30 min:

(1) 28/77
(2) 40/77

(2) 14/77

(2) 20/77

(2) Placebo, n = 77

(Continued)

HR - headache relief; IN - intranasal; n - number of participants; PF - pain-free; SC - subcutaneous

Appendix 6. Summary of outcomes: adverse events and withdrawals

Study ID	Treatment	Any AE	Serious AE	AE withdrawal	Other withdrawal
Bahra 2000	(1) Zolmitriptan 5 mg oral, n = 114 (2) Zolmitriptan 10 mg oral, n = 111 (3) Placebo, n = 115	Within 24 h: (1) 32/114 (2) 43/111 (3) 17/115 AE details reported for ITT population, not safety population	1 in (2), but 58 days after treatment, and not considered related	None in ITT population within 24 h of treatment One in safety population - no details	20 pts did not have three episodes
Cittadini 2006	(1) Zolmitriptan 5 mg IN, n = 65 (2) Zolmitriptan 10 mg IN, n = 63 (3) Placebo, n = 61	No data	None	(1) 1/65 (shortness of breath, vomiting, rheumatic pain)	6 pts lost to follow-up, 2 pts without clear reason after treating one episode
Ekbom 1991	(1) Sumatriptan 6 mg SC, n = 39 (2) Placebo, n = 39	No time specified: (1) 15/49 (2) 12/47	None reported	None	8 pts excluded due to protocol violations, 2 pts had only one episode
Ekbom 1993	(1) Sumatriptan 6 mg SC, n = 92 (2) Sumatriptan 12 mg SC, n = 88 (3) Placebo, n = 88	No time specified: (1) 34/101 (2) 42/94 (3) 15/96 (over 90% mild/mod)	None reported	(3) 1/101 (pressure on neck)	21 pts had only one episode
Rapoport 2007	(1) Zolmitriptan 5 mg IN, n = 52 (2) Zolmitriptan 10 mg IN, n = 49 (3) Placebo, n = 50	No time specified: (1) 13/52 (2) 16/49 (3) 8/50 (mild, non-specific, typical of triptans)	None	None	12 pts lost to follow-up, 5 withdrew consent, 9 did not have an episode
Van Vliet 2003	(1) Sumatriptan 20 mg IN, n = 77 (2) Placebo, n = 77	No data	None	No data	7 pts lost to follow-up, 10 treated attacks of mild intensity
AE - adverse event; IN - intranasal; ITT - intention-to-treat; n - number of participants; pts - participants; SC - subcutaneous					

Appendix 7. Summary of outcomes: specific adverse events

Study ID	Treatment	General	Nausea ± vomiting	Local reaction	Pain/stiffness/tightness	Temperature sensation	Feeling of heaviness	Dizziness	Somnolence
Bahra 2000	(1) Zolmitriptan 5 mg oral, n = 114 (2) Zolmitriptan 10 mg oral, n = 111 (3) Placebo, n = 115	Detailed list (ITT pop not safety pop) for pts with specific events occurring in > 2%, and all chest symptoms	(1) 6/114 (2) 4/111 (3) 2/115	Paresthesia (NB oral route): (1) 3/114 (2) 11/111 (3) 7/115 Most common AE	Pain: (1) 2/114 (2) 6/111 (3) 4/115 Tightness: (1) 3/114 (2) 4/111 (3) 2/115	Sweating: (1) 0/114 (2) 4/111 (3) 0/115	(1) 3/114 (2) 6/111 (3) 0/115	(1) 4/114 (2) 4/111 (3) 1/115	(1) 4/114 (2) 3/111 (3) 2/115
Cittadini 2006	(1) Zolmitriptan 5 mg IN, n = 65 (2) Zolmitriptan 10 mg IN, n = 63 (3) Placebo, n = 61	No details of specific AEs							
Ekbom 1991	(1) Sumatriptan 6 mg SC, n = 39 (2) Placebo, n = 39 Not self-administered (phys/nurse)	Primarily two types: 1. injection site reactions (pain, swelling, burning, erythema, tingling) 11/39, 7/39 2. neurologic symptoms (dizziness, tiredness, numbness of hands, tingling, paraesthesia, feeling of paralysis of face, cold and hot sensations) 12/39, 8/39							
Ekbom 1993	(1) Sumatriptan 6 mg SC, n = 92 (2) Sumatriptan 12 mg SC, n = 88 (3) Placebo, n = 88 Not self-administered (phys/nurse)	14 events of severe intensity (injection site reaction, flushing, sweating, warm sensation, malaise/fatigue, prickling sensation) Chest symptoms mild or moderate, resolve ≥ 30 min (pressure 2 suma 6 mg, tightness 1 suma 6 mg and 1 suma 12 mg) AEs in ≥ 5% of participants	(1) 5/101 (2) 6/94 (3) 1/96	Injection site reaction: (1) 7/101 (2) 9/94 (3) 4/96	(1) 1/101 (2) 5/94 (3) 0/96	(1) 5/101 (2) 3/94 (3) 1/96	(1) 5/101 (2) 5/94 (3) 1/96		

(Continued)

Rapoport 2007	(1) Zolmitriptan 5 mg IN, n = 52 (2) Zolmitriptan 10 mg IN, n = 49 (3) Placebo, n = 50	Mild, nonspecific, typical of triptan sensations	(1) 0/52 (2) 2/49 (3) 0/50	Bad taste: (1) 8/52 (2) 11/49 (3) 5/50 Discomfort of nasal cavity: (1) 4/52 (2) 6/49 (3) 3/50	Throat: (1) 1/52 (2) 2/49 (3) 1/50 Chest: (1) 1/52 (2) 1/49 (3) 0/50 Neck: (1) 2/52 (2) 2/49 (3) 0/50	(1) 2/52 (2) 2/49 (3) 1/50	(1) 3/52 (2) 4/49 (3) 2/50
Van Vliet 2003	(1) Sumatriptan 20 mg IN, n = 77 (2) Placebo, n = 77	Very limited data		Bitter taste: (1) 21% (2) 1% (most com- mon event)	Chest pres- sure: (1) 2/77 (2) 0/77		

IN - intranasal; n - number of participants; pts - participants; SC - subcutaneous

Appendix 8. Other outcomes

Pain-free at 60 minutes

Zolmitriptan

One study ([Rapoport 2007](#)) reported on participants who were pain-free at 60 minutes: 59% of attacks with intranasal zolmitriptan 10 mg, and 49% (estimated from graph) with intranasal zolmitriptan 5 mg were pain-free compared with 36% with placebo. There were insufficient data for analysis.

Sumatriptan

There were no studies of sumatriptan reporting on participants who were pain-free at times greater than 30 minutes.

Headache relief at 60 minutes

Zolmitriptan

One study ([Rapoport 2007](#)) reported on headache relief at 60 minutes: 80% (39/49) of attacks treated with intranasal zolmitriptan 10 mg, and 58% (30/52) treated with intranasal zolmitriptan 5 mg had headache relief compared with 56% (28/50) treated with placebo. There were insufficient data for analysis.

Sumatriptan

There were no studies of sumatriptan reporting on participants who had headache relief at times greater than 30 minutes.

Relief of headache-associated symptoms (zolmitriptan and sumatriptan)

Three studies ([Bahra 2000](#); [Cittadini 2006](#); [Van Vliet 2003](#)) reported on the percentage of attacks in which there was an 'improvement' in various symptoms commonly associated with cluster headache at 30 minutes after treatment. The percentage was of those with symptoms at baseline, but this baseline number was not reported. [Bahra 2000](#) gave data for participants with episodic-type headaches only. The symptoms were conjunctival injection or lacrimation, nasal congestion, ptosis or eyelid oedema, miosis and photophobia. Numerically, there was generally more improvement with triptan than placebo, and with zolmitriptan 10 mg than 5 mg, but it was not possible to assess the clinical significance of the differences observed.

[Ekblom 1991](#) reported the presence of conjunctival injection at 15 and 30 minutes, with substantial differences between treatment and placebo groups at both time points. [Ekblom 1993](#) reported the presence of conjunctival injection and 'normal function' at both baseline and 15 minutes. There were substantial improvements, of clinical relevance, for both outcomes in the treatment group.

Details of associated symptom outcomes for individual studies									
Study ID	Treatment	Definition	Conjunctival injection/lacrimation	Nasal congestion	Pto-sis/eyelid oedema	Forehead sweating	Miosis	Photo-phobia	Normal function (FD score ≥ 1)
Bahra 2000	(1) Zolmitriptan 5 mg oral, n = 114	Episodic pts only	(1) 40%	(1) 52%	(1) 41%	(1) 41%	Blurred vision	No data	No data
	(2) Zolmitriptan 10 mg oral, n = 111	Improvement at 30 min (from graph)	(2) 54%	(2) 60%	(2) 43%	(2) 49%	(1) 52%		
	(3) Placebo, n = 115	% of those with symptom at baseline (denominator not reported)	(3) 32%	(3) 32%	(3) 29%	(3) 36%	(2) 59%		
Cittadini 2006	(1) Zolmitriptan 5 mg IN, n = 65	Improvement at 30 min (from graph)	(1) 30.1%	(1) 27.8%	(1) 19.9%	(1) 13.0%	(1) 6.9%	No data	No data
	(2) Zolmitriptan 10 mg IN, n = 63	% of those with symptom at baseline (denominator not reported)	(2) 31.5%	(2) 33.8%	(2) 17.1%	(2) 14.8%	(2) 13.0%		
	(3) Placebo, n = 61		(3) 24.1%	(3) 24.1%	(3) 13.9%	(3) 12.0%	(3) 11.1%		
Ekbom 1991	(1) Sumatriptan 6 mg SC, n = 39	Symptom present at 15 and 30 min post-dose	15 min: (1) 36%						No usable data
	(2) Placebo, n = 39		(2) 74%						
Ekbom 1993	Not self-administered (phys/nurse)		30 min: (1) 10%						
	(1) Sumatriptan 6 mg SC, n = 92	Symptom present at 15 min post-dose	(2) 51%						
	(2) Sumatriptan 12 mg SC, n = 88	Baseline:	(1) 38% = 35/92						From graph
Rapoport 2007	(3) Placebo, n = 88	(1) 67/92	(2) 30% = 26/88						Baseline:
	Not self-administered (phys/nurse)	(2) 65/88	(3) 60% = 53/88						(1) 22%
		(3) 67/88							(2) 27.1%
									(3) 27.1%
									At 15 min:
									(1) 86.4%
									(2) 88.1%
									(3) 55.9%
Rapoport 2007	(1) Zolmitriptan 5 mg IN, n = 52	No data							
	(2) Zolmitriptan 10 mg IN, n = 49

(Continued)

(3) Placebo, n = 50

Van Vliet 2003	(1) Sumatriptan 20 mg IN, n = 77 (2) Placebo, n = 77	Improvement at 30 min (from graph) % of those with symp- tom at baseline (de- nominator not report- ed)	(1) 62.7% (2) 33.6%	(1) 68.7% (2) 49.3%	(1) 56% (2) 41.8%	(1) 74.6% (2) 44%	(1) 71.6% (2) 38.1%	(1) 70.1% (2) 52.2%	No data
IN - intranasal; n - number of participants; pts - participants; SC - subcutaneous									

Use of rescue medication

Details of use of rescue medication in individual studies are presented in [Appendix 5](#).

Zolmitriptan

Three studies provided data for zolmitriptan. One ([Bahra 2000](#)) used an oral, and two ([Cittadini 2006](#); [Rapoport 2007](#)) used an intranasal formulation. All tested both 5 mg and 10 mg doses; 231 attacks were treated with zolmitriptan 5 mg, 223 with zolmitriptan 10 mg, and 226 with placebo. [Bahra 2000](#) and [Cittadini 2006](#) permitted use of rescue medication (oxygen or analgesic) after 30 minutes, and [Rapoport 2007](#) after 60 minutes. There was no obvious difference in response rates between these two times, so we combined the results for analysis.

Analysis of the two studies using the intranasal formulation alone, or the two studies reporting at 30 minutes did not substantially change the result.

Sumatriptan

Two studies using subcutaneous sumatriptan provided data. Rescue medication (100% oxygen) was permitted after 15 minutes. [Ekblom 1991](#) used 6 mg, and [Ekblom 1993](#) used 6 mg and 12 mg. These studies were combined for analysis.

Analysis of the 6 mg dose alone did not substantially change the result.

[Van Vliet 2003](#), using intranasal sumatriptan 20 mg, permitted use of rescue medication (oxygen or analgesic) after 30 minutes, with 28/77 (36%) attacks with sumatriptan and 40/77 (52%) participants with placebo requiring rescue medication ([Appendix 5](#)). There were insufficient data for analysis.

Summary of results B: use of rescue medication							
Drug	Dose (mg)	Time (min)	Studies	Participants or Attacks	Triptan %	Placebo %	NNTp (95% CI)
Zolmitriptan	5	30	2	355	30	43	7.4 (4.3 to 27)
Zolmitriptan	5	60	1	102	31	38	Not calculated
Zolmitriptan	5	30, 60	3	457	30	42	8.2 (4.8 to 29) (Analysis 1.6)
Zolmitriptan	10	30	2	350	27	43	6.2 (3.8 to 16)
Zolmitriptan	10	60	1	99	27	42	Not calculated
Zolmitriptan	10	30, 60	3	449	27	42	6.8 (4.3 to 17) (Analysis 2.6)
Sumatriptan	6, 12	15	3	346	12	41	3.5 (2.6 to 5.3) (Analysis 4.4)
Sumatriptan	6	15	2	214	14	43	3.4 (2.4 to 5.7)
Sumatriptan	20	30	1	154	36	52	Not calculated

Recurrence

None of the included studies reported data on headache recurrence ([Appendix 5](#)).

WHAT'S NEW

Date	Event	Description
17 May 2018	Review declared as stable	See Published notes

HISTORY

Protocol first published: Issue 4, 2009

Review first published: Issue 4, 2010

Date	Event	Description
2 June 2016	Review declared as stable	See Published notes .
4 April 2013	New citation required but conclusions have not changed	No new studies identified.
4 April 2013	New search has been performed	New searches carried out, 'Risk of bias' tables expanded and updated, 'Summary of findings' table added.

CONTRIBUTIONS OF AUTHORS

For the original review, SL and SD carried out the searches, identified studies for inclusion, and extracted relevant data. SL, SD and RAM were involved in analysis. HJM acted as arbitrator. All review authors were involved with writing the protocol and the full review.

For the update, SL and SD checked for new studies and assessed additional criteria for the 'Risk of bias' table, SD revised the manuscript and all authors read and approved the update.

DECLARATIONS OF INTEREST

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

SOURCES OF SUPPORT

Internal sources

- Pain Research Funds, UK.
- General institutional support

External sources

- International Headache Society, Other.
- Funding for administrative costs associated with editorial and peer review

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the published protocol for this review, we stated that we would consider pain outcomes assessed at 30 minutes post-treatment or later. For the full review, we decided to include 15 minute data as well. Our reasoning was that since rapid relief is important in this disabling condition, including the 15 minute data would improve the relevance and usefulness of the review; four of the six included studies reported data for 15 minutes. Some data were available for other early time points (5, 10, 20 minutes) for some studies, but these were insufficient for analysis, and we felt they did not add significantly to our understanding of efficacy.

Relatively few pain outcomes were reported at 60 minutes post-treatment. Because of this, and because many cluster headache episodes may resolve spontaneously by 60 minutes, we have de-emphasised results for this time point in our descriptions of results for pain outcomes.

For the update we have expanded the 'Risk of bias' assessment and graph, and included a 'Summary of findings' table. We have also included an assessment of publication bias, which is now routine in PaPaS headache reviews.

After discussion with headache specialists and editorial staff, and in line with Cochrane recommendations, we decided to limit our outcomes for acute headache reviews in order to focus attention on the most important outcomes and to make the reviews more readable for both clinicians and patients. In this update we have moved results for use of rescue medication and relief of headache-associated symptoms to [Appendix 8](#).

NOTES

A restricted search in May 2018 did not identify any potentially relevant studies likely to change the conclusions. Therefore, this review has now been stabilised following discussion with the authors and editors. If appropriate, we will update the review if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.

INDEX TERMS

Medical Subject Headings (MeSH)

Cluster Headache [*drug therapy]; Oxazolidinones [therapeutic use]; Randomized Controlled Trials as Topic; Serotonin Receptor Agonists [*therapeutic use]; Sumatriptan [therapeutic use]; Tryptamines [*therapeutic use]

MeSH check words

Humans