ClinicalEvidence

Cluster headache

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ABSTRACT

INTRODUCTION: The revised International Headache Society (IHS) criteria for cluster headache are: attacks of severe or very severe, strictly unilateral pain, which is orbital, supraorbital, or temporal pain, lasting 15 to 180 minutes and occurring from once every other day to eight times daily. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of interventions to abort cluster headache? What are the effects of interventions to prevent cluster headache? We searched: Medline, Embase, The Cochrane Library, and other important databases up to June 2009 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations, such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 23 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review, we present information relating to the effectiveness and safety of the following interventions: baclofen (oral); botulinum toxin (intramuscular); capsaicin (intranasal); chlorpromazine; civamide (intranasal); clonidine (transdermal); corticosteroids; ergotamine and dihydroergotamine (oral or intranasal); gabapentin (oral); greater occipital nerve injections (betamethasone plus xylocaine); high-dose and high-flow-rate oxygen; hyperbaric oxygen; leuprolide; lidocaine (intranasal); lithium (oral); melatonin; methysergide (oral); octreotide (subcutaneous); pizotifen (oral); sodium valproate (oral); sumatriptan (oral, subcutaneous, and intranasal); topiramate (oral); tricyclic antidepressants (TCAs); verapamil; and zolmitriptan (oral and intranasal).

QUESTIONS

INTERVENTIONS

TREATMENTS TO ABORT HEADACHE

TREATMENTS TO PREVENT CLUSTER HEADACHE

Footnote

*Categorisation based on consensus.

Key points

- The revised International Headache Society (IHS) criteria for cluster headache are: attacks of severe or very severe, strictly unilateral pain, which is orbital, supraorbital, or temporal pain, lasting 15 to 180 minutes and occurring from once every other day to eight times daily. The attacks are associated with one or more of the following, all of which are ipsilateral: conjunctival injection, lacrimation, nasal congestion, rhinorrhoea, forehead and facial sweating,

miosis, ptosis, and eyelid oedema. Most people are restless or agitated during an attack. Cluster headache may be episodic or chronic.

Cluster headache is rare, but the exact prevalence remains a matter of debate.

- The main focus of intervention is to abort attacks once they have begun and to prevent future attacks.
- Sumatriptan, used subcutaneously or intranasally, and zolmitriptan used intranasally reduce the severity and duration of cluster headache attacks once they have begun.

  Oral zolmitriptan reduces severity of attacks in people with episodic cluster headache, but we don't know how effective it is in people with chronic cluster headache.

  We don't know whether oral sumatriptan is effective.
- There is consensus that high-dose and high-flow-rate oxygen is effective for abortive treatment of episodic or chronic cluster headache. We don't know whether this consensus can be applied to hyperbaric oxygen, as little research has been conducted.
- There is also consensus that subcutaneous octreotide is effective for abortive treatment of cluster headache.
- We don't know whether intranasal lidocaine is effective for abortive treatment of cluster headache.
- There is consensus that both verapamil and lithium prevent cluster headache, but that verapamil is more effective than lithium, and causes fewer adverse effects.

  There is also consensus that corticosteroids and greater occipital nerve injections (betamethasone plus xylocaine) are effective for preventive treatment.
- We don't know whether baclofen, botulinum toxin, capsaicin, chlorpromazine, civamide, clonidine, ergotamine or dihydroergotamine, gabapentin, leuprolide, melatonin, methysergide, pizotifen, sodium valproate, oral sumatriptan, topiramate, or tricyclic antidepressants are effective for prevention of cluster headache. Some of these interventions are not routinely used in clinical practice.

DEFINITION

The revised International Headache Society (IHS) criteria for cluster headache are: attacks of severe or very severe, strictly unilateral pain, which is orbital, supraorbital, or temporal pain, lasting 15 to 180 minutes, and occurring from once every other day to eight times daily (see table 1, p 37 for full details). [1] The attacks are associated with at least one of the following cranial autonomic features, all of which are ipsilateral: conjunctival injection, lacrimation, nasal congestion, rhinorrhoea, forehead and facial sweating, miosis, ptosis, and eyelid oedema. The revised IHS criteria allow the diagnosis of cluster headache to be made in the absence of ipsilateral cranial autonomic features, provided the person reports a sense of restlessness or agitation. Attacks usually occur in series (cluster periods) lasting for weeks or months, separated by remission periods usually lasting months or years. However, about 10% to 15% of people have chronic symptoms without remissions. Cluster headache is further subclassified according to the duration of the bout. Episodic cluster headache is diagnosed when cluster headache attacks occur in periods lasting 7 days to 1 year, separated by remissions lasting 1 month or longer. Chronic cluster headache is diagnosed when cluster headache attacks occur for more than 1 year without remission, or with remissions lasting less than 1 month. The term cluster headache is now widely accepted, although historically the condition has been known by several different names, including: migrainous neuralgia, Horton's headache, histaminic cephalalgia, sphenopalatine neuralgia, Sluder's neuralgia, petrosal neuralgia, red migraine, erythroprosopalgia of Bing, ciliary neuralgia, erythromelalgia of the head, Vidian neuralgia, hemicrania angioparalytica, hemicrania periodic neuralgiforms, syndrome of hemicephalic vasodilation of sympathetic origin, and autonomic faciocephalalgia.

INCIDENCE/ PREVALENCE

Cluster headache is rare, but the exact prevalence remains a matter of debate because of the remarkable variation of the estimated prevalence — between 56 and 401 per 100,000 population — in the various studies. [2] [3] [4] [5] [6] [7] Recent studies suggest that the prevalence of cluster headache is likely to be at least one person per 500. [8] Cluster headache is more prevalent in men. The gender ratio in the various case series varies between 2.5:1 and 7.2:1. [9] [10] [11] [12] [13] [14] [15] [16] [17]

AETIOLOGY/ RISK FACTORS

There is a small increased familial risk of cluster headache, suggesting a genetic role in causation. [18] People with cluster headache may over indulge in non-essential consumption habits [11] [19] [20] including smoking, [16] [17] intake of alcohol, [21] [22] and consumption of coffee. [23] There is an increased incidence of previous head trauma in cluster headache, ranging between 5% and 37%, although there is often a long interval between the head trauma and the onset of the headaches. [11] [23] [24] [25]

PROGNOSIS

Onset of symptoms most commonly occurs between the second and fourth decades of life, [14] [16] [18] although cluster headache has been reported in all age groups. Although there is a paucity of literature on the long-term prognosis of cluster headache, the available evidence suggests

that it is a lifelong disorder in most people. In one study, episodic cluster headache (ECH) evolved into chronic cluster headache (CCH) in about 10% of people, whereas CCH transformed into ECH in one third of people. [26] Furthermore, a substantial proportion of people with cluster headache can expect to develop longer remission periods with increasing age. [27]

AIMS OF INTERVENTION To reduce frequency, severity, and duration of headache once attacks have begun (abortive treatment) and to prevent attacks (preventive treatment), with minimal adverse effects from treatment; to improve quality of life.

OUTCOMES Headache relief (measured by headache frequency, headache severity, and headache duration).

METHODS *Clinical Evidence* search and appraisal June 2009. The following databases were used to identify studies for this systematic review: Medline 1966 to June 2009, Embase 1980 to June 2009, and The Cochrane Database of Systematic Reviews, Issue 2, 2009 (1966 to date of issue). An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language, at least single blinded, and containing any number of individuals of whom more than 60% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as "open", "open label", or not blinded, unless blinding was impossible. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. In addition, we did an observational harms search for specific harms as highlighted by the contributor, peer reviewer, and editor. We searched for observational studies assessing cerebrovascular adverse effects of triptans, cardiovascular adverse effects of verapamil, and visceral fibrosis/scleroderma as an adverse effect of methysergide. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 38). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of interventions to abort cluster headache?

OPTION SUMATRIPTAN (SUBCUTANEOUS AND INTRANASAL) FOR ABORTING CLUSTER HEADACHE

- For GRADE evaluation of interventions for Cluster headache, see table, p 38 .
- Sumatriptan, used subcutaneously or intranasally, reduces the severity and duration of cluster headache attacks once they have begun.
- We found no direct information from RCTs about oral sumatriptan for the abortive treatment of episodic or chronic cluster headaches.

Benefits and harms

Subcutaneous sumatriptan versus placebo:

We found one systematic review (search date 1998), [28] which identified two RCTs. [29] [30] The review did not carry out a meta-analysis. The searches in the systematic review were restricted to English language studies.

Headache relief

Subcutaneous sumatriptan compared with placebo Subcutaneous sumatriptan may be more effective at reducing the severity and duration of headache at 15 minutes in people with episodic or chronic cluster headaches (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Headache relief					
[29] RCT **Crossover design**	49 people with episodic or chronic cluster headache In review [28]	**Headache relief , 15 minutes** 29/39 (74%) attacks with subcutaneous sumatriptan (6 mg) 10/39 (26%) attacks with placebo In total, 39/49 (80%) people completed the study: analysis was not by intention to treat See further information on studies for definition of headache relief	P <0.001	○○○	subcutaneous sumatriptan
[30] RCT **Crossover design** **3-armed trial**	157 people with episodic or chronic cluster headache admitted to hospital for treatment In review [28] The third arm evaluated subcutaneous sumatriptan 6 mg	**Headache relief , 10 minutes** 63% with subcutaneous sumatriptan 12 mg 25% with placebo Absolute numbers not reported Only people who completed crossover were included in the analysis See further information on studies for definition of headache relief	P <0.01 for sumatriptan 12 mg *v* placebo	○○○	subcutaneous sumatriptan
[30] RCT **Crossover design** **3-armed trial**	157 people with episodic or chronic cluster headache admitted to hospital for treatment In review [28] The third arm evaluated subcutaneous sumatriptan 12 mg	**Headache relief , 10 minutes** 49% with subcutaneous sumatriptan 6 mg 25% with placebo Absolute numbers not reported Only people who completed crossover were included in the analysis See further information on studies for definition of headache relief	P <0.01 for sumatriptan 6 mg *v* placebo	○○○	subcutaneous sumatriptan
[30] RCT **Crossover design** **3-armed trial**	157 people with episodic or chronic cluster headache admitted to hospital for treatment In review [28] The third arm evaluated subcutaneous sumatriptan 6 mg	**Headache relief , 15 minutes** 80% with subcutaneous sumatriptan 12 mg 35% with placebo Absolute numbers not reported Only people who completed crossover were included in the analysis See further information on studies for definition of headache relief	P <0.01 for sumatriptan 12 mg *v* placebo	○○○	subcutaneous sumatriptan
[30] RCT **Crossover design** **3-armed trial**	157 people with episodic or chronic cluster headache admitted to hospital for treatment In review [28] The third arm evaluated subcutaneous sumatriptan 12 mg	**Headache relief , 15 minutes** 75% with subcutaneous sumatriptan 6 mg 35% with placebo Absolute numbers not reported Only people who completed crossover were included in the analysis See further information on studies for definition of headache relief	P <0.01 for sumatriptan 6 mg *v* placebo	○○○	subcutaneous sumatriptan

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Resolution of attacks					
[29] RCT **Crossover design**	49 people with episodic or chronic cluster headache In review [28]	**Attacks resolved , 30 minutes** 77% with subcutaneous sumatriptan (6 mg) 49% with placebo Absolute numbers not reported In total, 39/49 (80%) people completed the study: analysis was not by intention to treat	P = 0.004	○○○	subcutaneous sumatriptan

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[29] RCT **Crossover design**	49 people with episodic or chronic cluster headache In review [28]	**Adverse effects** 17/49 (35%) with subcutaneous sumatriptan (6 mg) 12/47 (26%) with placebo In total, 39/49 (80%) people completed the study: analysis was not by intention to treat	Significance not assessed		
[29] RCT **Crossover design**	49 people with episodic or chronic cluster headache In review [28]	**Injection-site reactions** 11/49 (22%) with subcutaneous sumatriptan (6 mg) 7/47 (15%) with placebo In total, 39/49 (80%) people completed the study: analysis was not by intention to treat	Significance not assessed		
[29] RCT **Crossover design**	49 people with episodic or chronic cluster headache In review [28]	**Neurological symptoms** 12/49 (24%) with subcutaneous sumatriptan (6 mg) 8/47 (17%) with placebo Symptoms included dizziness, tiredness, numbness of hands, tingling, paraesthesia, a feeling of paralysis in the face, and cold and hot sensations In total, 39/49 (80%) people completed the study: analysis was not by intention to treat	Significance not assessed		
[30] RCT **Crossover design** **3-armed trial**	157 people with episodic or chronic cluster headache admitted to hospital for treatment In review [28]	**Adverse effects** 32/94 (45%) with subcutaneous sumatriptan 12 mg 34/101 (34%) with subcutaneous sumatriptan 6 mg 15/96 (16%) with placebo Only people who completed crossover were included in the analysis	Significance not assessed		
[30] RCT	157 people with episodic or chronic cluster headache	**Pressure sensation on the head, neck, or right temple**	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Crossover design **3-armed trial**	admitted to hospital for treatment In review [28]	3/94 (3%) with subcutaneous sumatriptan 12 mg 5/101 (5%) with subcutaneous sumatriptan 6 mg 1/96 (1%) with placebo Only people who completed crossover were included in the analysis			
[30] RCT **Crossover design** **3-armed trial**	157 people with episodic or chronic cluster headache admitted to hospital for treatment In review [28]	**Feeling of heaviness** 5/94 (5%) with subcutaneous sumatriptan 12 mg 5/101 (5%) with subcutaneous sumatriptan 6 mg 1/96 (1%) with placebo Only people who completed crossover were included in the analysis	Significance not assessed		

Intranasal sumatriptan versus placebo:

We found no systematic review, but found one double-blind crossover RCT. [31]

Headache relief

Intranasal sumatriptan compared with placebo Intranasal sumatriptan may be more effective at reducing pain at 30 minutes, at reducing the duration of attacks, and at relieving the number of attacks in people with episodic or chronic cluster headache (low quality-evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Headache relief					
[31] RCT **Crossover design**	118 people; 75% with episodic cluster headache; 25% with chronic cluster headache; 154 attacks were treated	**Headache relief , 30 minutes** 44/77 (57%) attacks with intranasal sumatriptan (20 mg) 20/77 (26%) attacks with placebo See further information on studies for details on RCT protocol	P = 0.002	○○○	intranasal sumatriptan
Freedom from pain					
[31] RCT **Crossover design**	118 people; 75% with episodic cluster headache; 25% with chronic cluster headache; 154 attacks were treated	**Pain free , 30 minutes** 36/77 (47%) attacks with intranasal sumatriptan (20 mg) 14/77 (18%) attacks with placebo See further information on studies for details on RCT protocol	P = 0.003	○○○	intranasal sumatriptan
Time to relief					
[31] RCT **Crossover design**	118 people; 75% with episodic cluster headache; 25% with chronic cluster headache; 154 attacks were treated	**Mean time to initial relief** 12.4 minutes with intranasal sumatriptan (20 mg) 17.6 minutes with placebo See further information on studies for details on RCT protocol	P = 0.01	○○○	intranasal sumatriptan

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[31] RCT **Crossover design**	118 people; 75% with episodic cluster headache; 25% with chronic cluster headache; 154 attacks were treated	**Adverse effects** with intranasal sumatriptan (20 mg) with placebo The RCT reported no serious adverse effects. Two people (3%) using sumatriptan reported chest pressure after using the nasal spray The most frequently reported adverse effect was a bitter taste after using the nasal spray (21% with sumatriptan *v* 1% with placebo) See further information on studies for details on RCT protocol			

Further information on studies

[29] Headache severity in the RCT was assessed using a pain scale ranging from 0 (no pain) to 4 (very severe pain). Headache relief was measured as a decrease in the severity of headache to grade 1 or 0 (from a pretreatment grade of 2, 3, or 4).

[30] Headache severity was assessed using a pain scale ranging from 0 (no pain) to 4 (very severe pain), and headache relief was defined as a change from pretreatment grade 2, 3, or 4 to grade 1 or 0.

[31] Headache response at 30 minutes was defined as a reduction in headache severity from very severe, severe, or moderate, to nil or mild. The method of randomisation was not reported. People treated two headache attacks at least 24 hours apart with either sumatriptan 20 mg or placebo, and then used the alternative treatment for two further headache attacks. The 24-hour delay between crossover of treatments would have allowed washout preventing carry-over effects in the post-crossover analysis.

Comment: None.

OPTION ZOLMITRIPTAN (INTRANASAL) FOR ABORTING CLUSTER HEADACHE New

- For GRADE evaluation of interventions for Cluster headache, see table, p 38 .
- Zolmitriptan used intranasally, p 7 reduces the severity and duration of cluster headache attacks once they have begun.

Benefits and harms

Intranasal zolmitriptan versus placebo:

We found no systematic review, but found two double-blind crossover RCTs. [32] [33] Both RCTs used a 5-point ordinal scale (none, mild, moderate, severe, or very severe) to assess headache severity before and after treatment. Headache relief was defined as a reduction in headache from very severe, severe, or moderate, to mild or none.

Headache relief

Intranasal zolmitriptan compared with placebo Intranasal zolmitriptan 5 mg and 10 mg may be more effective at increasing relief from headache and reducing pain at 30 minutes in people with episodic or chronic cluster headaches (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Headache response					
[32] RCT **Crossover design** **3-armed trial**	92 people; 59 (64%) with episodic cluster headache and 33 (36%) with chronic cluster headache; 189 attacks in total The third arm evaluated intranasal zolmitriptan 5 mg	**Headache response , 30 minutes** 38/63 (61%) attacks with zolmitriptan 10 mg 14/61 (23%) attacks with placebo Of 92 people recruited, 69 (70%) people treated their first cluster headache attack and were available for intention-to-treat analysis See further information on studies for definition of headache response	P <0.002 for intranasal zolmitriptan 10 mg *v* placebo The method of randomisation was not reported	○○○	intranasal zolmitriptan
[32] RCT **Crossover design** **3-armed trial**	92 people; 59 (64%) with episodic cluster headache and 33 (36%) with chronic cluster headache; 189 attacks in total The third arm evaluated intranasal zolmitriptan 10 mg	**Headache response , 30 minutes** 27/65 (42%) attacks with zolmitriptan 5 mg 14/61 (23%) attacks with placebo Of 92 people recruited, 69 (70%) people treated their first cluster headache attack and were available for intention-to-treat analysis See further information on studies for definition of headache response	P <0.002 for intranasal zolmitriptan 5 mg *v* placebo The method of randomisation was not reported	○○○	intranasal zolmitriptan
[33] RCT **Crossover design** **3-armed trial**	78 people; 52 people treating first cluster headache attack, 37 (71%) had episodic cluster headache, and 15 (29%) had chronic cluster headache; 151 attacks in total The remaining arm evaluated intranasal zolmitriptan 5 mg	**Headache response , 10 minutes** 25% (attacks) with zolmitriptan 10 mg 10% (attacks) with placebo Absolute numbers not reported Time at which zolmitriptan 10 mg was measured as significantly more effective at improving headache compared with placebo Of 78 people recruited, 52 (67%) treated their first cluster headache attack and were available for intention-to-treat analysis	P <0.05	○○○	intranasal zolmitriptan
[33] RCT **Crossover design** **3-armed trial**	78 people; 52 people treating first cluster headache attack, 37 (71%) had episodic cluster headache, and 15 (29%) had chronic cluster headache; 151 attacks in total The remaining arm evaluated intranasal zolmitriptan 10 mg	**Headache response , 20 minutes** 39% attacks with zolmitriptan 5 mg 20% attacks with placebo Absolute numbers not reported Time at which zolmitriptan 5mg was measured as significantly more effective at improving headache compared with placebo Of 78 people recruited, 52 (67%) treated their first cluster headache attack and were available for intention-to-treat analysis	P <0.01	○○○	intranasal zolmitriptan

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[33] RCT **Crossover design** **3-armed trial**	78 people; 52 people treating first cluster headache attack, 37 (71%) had episodic cluster headache, and 15 (29%) had chronic cluster headache; 151 attacks in total The remaining arm evaluated intranasal zolmitriptan 5 mg	**Headache response , 30 minutes** 31/49 (63%) attacks with zolmitriptan 10 mg 15/50 (30%) attacks with placebo 99 attacks in this analysis	P <0.01	○○○	intranasal zolmitriptan
[33] RCT **Crossover design** **3-armed trial**	78 people; 52 people treating first cluster headache attack, 37 (71%) had episodic cluster headache, and 15 (29%) had chronic cluster headache; 151 attacks in total The remaining arm evaluated intranasal zolmitriptan 10 mg	**Headache response , 30 minutes** 26/52 (50%) attacks with zolmitriptan 5 mg 15/50 (30%) attacks with placebo 102 attacks in this analysis	P <0.05	○○○	intranasal zolmitriptan
Freedom from pain					
[32] RCT **Crossover design** **3-armed trial**	92 people; 59 (64%) with episodic cluster headache and 33 (36%) with chronic cluster headache; 189 attacks in total The third arm evaluated zolmitriptan 5 mg	**Free from pain , 30 minutes** 31/63 (50%) attacks with zolmitriptan 10 mg 10/61 (16%) attacks with placebo Of 92 people recruited, 69 (70%) people treated their first cluster headache attack and were available for intention-to-treat analysis See further information on studies for definition of headache response	P <0.003 for intranasal zolmitriptan 10 mg *v* placebo The method of randomisation was not reported	○○○	intranasal zolmitriptan
[32] RCT **Crossover design** **3-armed trial**	92 people; 59 (64%) with episodic cluster headache and 33 (36%) with chronic cluster headache; 189 attacks in total The third arm evaluated zolmitriptan 10 mg	**Free from pain , 30 minutes** 18/65 (28%) attacks with zolmitriptan 5 mg 10/61 (16%) attacks with placebo Of 92 people recruited, 69 (70%) people treated their first cluster headache attack and were available for intention-to-treat analysis See further information on studies for definition of headache response	P <0.003 for intranasal zolmitriptan 5 mg *v* placebo The method of randomisation was not reported	○○○	intranasal zolmitriptan
[33] RCT **Crossover design** **3-armed trial**	78 people; 52 people treating first cluster headache attack, 37 (71%) had episodic cluster headache, and 15 (29%) had chronic cluster headache; 151 attacks in total	**Free from pain , 30 minutes** 47% attacks with zolmitriptan 10 mg 20% attacks with placebo Absolute numbers not reported Of 78 people recruited, 52 (67%) treated their first cluster headache attack and were available for intention-to-treat analysis	P <0.01 for intranasal zolmitriptan 10 mg *v* placebo	○○○	intranasal zolmitriptan

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	The third arm evaluated zolmitriptan 5 mg				
[33] RCT **Crossover design** **3-armed trial**	78 people; 52 people treating first cluster headache attack, 37 (71%) had episodic cluster headache, and 15 (29%) had chronic cluster headache; 151 attacks in total The third arm evaluated zolmitriptan 10 mg	**Free from pain , 30 minutes** 39% attacks with zolmitriptan 5 mg 20% attacks with placebo Absolute numbers not reported Of 78 people recruited, 52 (67%) treated their first cluster headache attack and were available for intention-to-treat analysis	P <0.01 for intranasal zolmitriptan 5 mg *v* placebo	○○○	intranasal zolmitriptan

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[32] RCT **Crossover design** **3-armed trial**	92 people; 59 (64%) with episodic cluster headache and 33 (36%) with chronic cluster headache; 189 attacks in total	**Adverse effects** with zolmitriptan 10 mg with zolmitriptan 5 mg with placebo Of 92 people recruited, 69 (70%) people treated their first cluster headache attack and were available for intention-to-treat analysis The RCT gave no comparative data on adverse effects It reported no serious adverse effects in either the zolmitriptan or placebo arms One person withdrew because of development of shortness of breath, vomiting, and rheumatic pain associated with intranasal zolmitriptan 5 mg	The method of randomisation was not reported		
[33] RCT **Crossover design** **3-armed trial**	78 people; 52 people treating first cluster headache attack, 37 (71%) had episodic cluster headache, and 15 (29%) had chronic cluster headache; 151 attacks in total	**Adverse effects** 33% with zolmitriptan 10 mg 25% with zolmitriptan 5 mg 16% with placebo Absolute numbers not reported Adverse effects reported included discomfort in nasal cavity and bad taste The RCT reported that adverse effects were mild, non-specific, and typical of the effects associated with triptans Of 78 people recruited, 52 (67%) treated their first cluster headache attack and were available for intention-to-treat analysis	P <0.05 for both intranasal zolmitriptan 10 mg and 5 mg *v* placebo	○○○	placebo

Further information on studies

[32] Headache response was defined as at least a 2-point reduction on a 5-point pain-intensity scale at 30 minutes.

Comment: None.

OPTION HIGH-DOSE AND HIGH-FLOW-RATE OXYGEN

- For GRADE evaluation of interventions for Cluster headache, see table, p 38 .
- There is consensus that high-dose and high-flow-rate oxygen, p 11 is effective for abortive treatment of episodic or chronic cluster headache.

Benefits and harms

High-dose and high-flow-rate oxygen versus placebo:

We found two systematic reviews (search date 1998 [28] and 2008), [34] both of which identified the same RCT. [35]

Headache relief

High-dose and high-flow-rate oxygen compared with placebo (air) High-dose and high-flow-rate oxygen may be more effective at relieving pain in people with a cluster headache (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Headache relief					
[35] RCT **Crossover design**	19 men with cluster headache In review [28] [34]	**Complete or substantial relief in 80% or more of attacks** 9/16 (56%) with oxygen (100% at 6 L/minute for up to 15 minutes) 1/14 (7%) with air See further information on studies for details of study protocol	RR 7.88 95% CI 1.13 to 54.66 RR calculated by review [34] See further information on studies for methodological issues	●●●	oxygen
[35] RCT **Crossover design**	19 men with cluster headache In review [28] [34]	**Average pain relief score** 1.93 with oxygen (100% at 6 L/minute for up to 15 minutes) 0.77 with air See further information about studies for details of study protocol and scoring of pain relief	P <0.01 See further information on studies for methodological issues	○○○	oxygen

Adverse effects

No data from the following reference on this outcome. [28] [34] [35]

Further information on studies

[35] The RCT used classification criteria for cluster headache defined by the Ad Hoc Committee on Classification of Headache, [36] as the trial predates the International Headaches Society classification criteria. Pain relief was assessed using a pain relief score (0 = no relief, 1 = slight relief, 2 = substantial relief, and 3 = complete relief). Each person was treated with either oxygen or air for a maximum of six individual cluster headaches, after which the alternative treatment was given. Eleven people used both gases (6 people improved and did not complete the crossover; 2 people were given the same gas both times). Method of randomisation was not reported. The RCT did not carry out a statistical assessment.

Comment:

Clinical guide:
There is consensus based on observational evidence that high-dose and high-flow-rate oxygen reduces the severity of attacks in people with episodic or chronic cluster headache. [37] The advantage of oxygen inhalation treatment is that it has no established adverse effects. It can be readily combined with other abortive and preventive treatments. It can be used several times daily, as opposed to subcutaneous or intranasal triptans, which can be used only up to a maximum of two (subcutaneous) or three (intranasal) times daily. The main drawback with oxygen inhalation treatment is the practical limitation imposed by the bulky equipment, and, although small portable cylinders are available, most people find these cumbersome and inconvenient. Furthermore, it forces the person to sit still during treatment — a behaviour usually incompatible with the excruciating pain of cluster headache. Some people are unable to hold the face mask against the face, as skin contact worsens the pain. People need to be cautioned that oxygen is highly combustible, and fire precautions need to be observed: in particular, the danger of smoking needs to be pointed out.

OPTION OCTREOTIDE (SUBCUTANEOUS)

- For GRADE evaluation of interventions for Cluster headache, see table, p 38 .
- There is consensus that subcutaneous octreotide is effective for abortive treatment of cluster headache.

Benefits and harms

Subcutaneous octreotide versus placebo:

We found no systematic review. We found one crossover RCT. [38]

Headache relief

Subcutaneous octreotide compared with placebo Subcutaneous octreotide seems more effective at relieving headache at 30 minutes in people with episodic or chronic cluster headaches (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Headache relief					
[38] RCT **Crossover design**	57 people; 41 (72%) with episodic cluster headache, 15 (26%) with chronic cluster headache, and 1 (2%) unclassifiable	**Headache relief , 30 minutes** 24/46 (52%) with octreotide 100 micrograms 16/45 (36%) with placebo See further information on studies for scoring of headache severity	P <0.01	○○○	octreotide
Freedom from pain					
[38] RCT **Crossover design**	57 people; 41 (72%) with episodic cluster headache, 15 (26%) with chronic cluster headache, and 1 (2%) unclassifiable	**Pain free , 30 minutes** 15/46 (33%) with octreotide 100 micrograms 6/45 (13%) with placebo	P = 0.04	○○○	octreotide

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Time to pain relief					
[38] RCT **Crossover design**	57 people; 41 (72%) with episodic cluster headache, 15 (26%) with chronic cluster headache, and 1 (2%) unclassifiable	**Mean time to initial relief** 18.3 minutes with octreotide 100 micrograms 18.1 minutes with placebo	Significance not assessed		

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[38] RCT **Crossover design**	57 people; 41 (72%) with episodic cluster headache, 15 (26%) with chronic cluster headache, and 1 (2%) unclassifiable	**Adverse effects** with octreotide 100 micrograms with placebo The RCT reported no serious adverse effects Eight (17%) people given octreotide reported minor GI disturbance, including nausea, abdominal bloating, and diarrhoea, compared with four (9%) people given placebo			

Further information on studies

[38] The severity of headache before and after treatment was assessed using an ordinal scale of headache severity (none, mild, moderate, severe, or very severe). Headache relief was defined as a reduction in headache from very severe, severe, or moderate, to mild or nil.

Comment: **Clinical guide:**
There is consensus based on observational evidence that octreotide is effective. [37]

OPTION ZOLMITRIPTAN (ORAL) FOR ABORTING CLUSTER HEADACHE

- For GRADE evaluation of interventions for Cluster headache, see table, p 38 .
- Oral zolmitriptan, p 13 reduces severity of attacks in people with episodic cluster headache, but we don't know how effective it is in people with chronic cluster headache.

Benefits and harms

Oral zolmitriptan versus placebo:

We found no systematic review. We found one double-blind crossover RCT comparing oral zolmitriptan 10 mg, oral zolmitriptan 5 mg, and placebo for the treatment of acute attacks. [39]

Headache relief

Oral zolmitriptan compared with placebo Oral zolmitriptan at both 5 mg and 10 mg may be more effective at relieving pain at 30 minutes in people with episodic cluster headache, and zolmitriptan 10 mg may be more effective at reducing headache severity. However, we don't know whether oral zolmitriptan is more effective at relieving chronic cluster headaches (low-quality evidence)

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Headache response					
[39] RCT **Crossover design** **3-armed trial**	91 (73%) people with episodic cluster headache Subgroup analysis Total population of 124 people with 340 attacks The remaining arm evaluated zolmitriptan 5 mg	**Headache response , 30 minutes** 47% with zolmitriptan 10 mg 29% with placebo Absolute numbers not reported For full details of how headache response was defined, see further information about studies	P = 0.02	○○○	zolmitriptan
[39] RCT **Crossover design** **3-armed trial**	91 (73%) people with episodic cluster headache Subgroup analysis Total population of 124 people with 340 attacks The remaining arm evaluated zolmitriptan 10 mg	**Headache response , 30 minutes** 40% with zolmitriptan 5 mg 19% with placebo Absolute numbers not reported For full details of how headache response was defined, see further information about studies	Reported as not significant P value not reported	⟷	Not significant
[39] RCT **Crossover design** **3-armed trial**	33 (27%) people with chronic cluster headache Subgroup analysis Total population of 124 people with 340 attacks	**Headache response , 30 minutes** 25% with zolmitriptan 10 mg 16% with zolmitriptan 5 mg 31% with placebo Absolute numbers not reported For full details of how headache response was defined, see further information about studies	Among group difference reported as not significant P value not reported	⟷	Not significant
Freedom from pain					
[39] RCT **Crossover design** **3-armed trial**	91 (73%) people with episodic cluster headache Subgroup analysis Total population of 124 people with 340 attacks The third arm evaluated zolmitriptan 5 mg	**Mild or no pain , 30 minutes** 47/79 (60%) with zolmitriptan 10 mg 35/83 (42%) with placebo	P <0.01 for zolmitriptan 10 mg *v* placebo	○○○	zolmitriptan
[39] RCT **Crossover design** **3-armed trial**	91 (73%) people with episodic cluster headache Subgroup analysis Total population of 124 people with 340 attacks The third arm evaluated zolmitriptan 10 mg	**Mild or no pain , 30 minutes** 47/83 (57%) with zolmitriptan 5 mg 35/83 (42%) with placebo	P <0.01 for zolmitriptan 5 mg *v* placebo	○○○	zolmitriptan

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[39] RCT **Crossover design** **3-armed trial**	33 (27%) people with chronic cluster headache Subgroup analysis Total population of 124 people with 340 attacks The third arm evaluated zolmitriptan 5 mg	**Mild or no pain , 30 minutes** 12/32 (38%) with zolmitriptan 10 mg 15/32 (47%) with placebo	Reported as not significant (zolmitriptan 10 mg *v* placebo) P value not reported	⟷	Not significant
[39] RCT **Crossover design** **3-armed trial**	33 (27%) people with chronic cluster headache Subgroup analysis Total population of 124 people with 340 attacks The third arm evaluated zolmitriptan 10 mg	**Mild or no pain , 30 minutes** 15/31 (48%) with zolmitriptan 5 mg 15/32 (47%) with placebo	Reported as not significant (zolmitriptan 5 mg *v* placebo) P value not reported	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[39] RCT **Crossover design** **3-armed trial**	124 people; 91(73%) with episodic cluster headache, 33 (27%) with chronic cluster headache; 340 attacks in total	**Adverse effects** 37/111 (33%) with zolmitriptan 10 mg 25/114 (22%) with zolmitriptan 5 mg 15/115 (13%) with placebo	Significance not assessed		
[39] RCT **Crossover design** **3-armed trial**	124 people; 91 (73%) with episodic cluster headache, 33 (27%) with chronic cluster headache; 340 attacks in total	**Chest symptoms (including tightness, heaviness, or pressure)** 4/111 (3.6%) with zolmitriptan 10 mg 1/114 (<1%) with zolmitriptan 5 mg 4/115 (3.5%) with placebo Chest symptoms were mainly of mild to moderate severity, short duration, and did not result in the people withdrawing from the study	Significance not assessed		

Further information on studies

[39] Headache response was defined as at least a 2-point reduction on a 5-point pain-intensity scale at 30 minutes. Follow-up in the RCT was 73%, but analysis was by intention to treat.

Comment: None.

OPTION HYPERBARIC OXYGEN

- For GRADE evaluation of interventions for Cluster headache, see table, p 38 .
- We don't know whether hyperbaric oxygen, p 16 is effective for abortive treatment of episodic or chronic cluster headache, as little research has been conducted.

Benefits and harms

Hyperbaric oxygen therapy versus placebo:

We found two systematic reviews (search dates 1998 [28] and 2008), [34] both of which identified the same controlled clinical trial. [40] The double-blind controlled clinical trial compared hyperbaric oxygen therapy (HBOT) versus placebo. [40]

Headache relief

Hyperbaric oxygen compared with placebo Hyperbaric oxygen may be more effective at reducing the duration of attacks and at relieving pain at 13 minutes in people with episodic cluster headaches (very low-quality evidence)

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Headache relief					
[40] Controlled clinical trial	13 people with episodic cluster headache 10 to 15 days into a cluster bout In review [28] [34]	**Interruption of attack , 5 to 13 minutes** 6/7 (86%) with HBOT 0/6 (0%) with placebo See further information on studies for full details on treatments and for information on improvement from baseline with HBOT	RR 11.38 95% CI 0.77 to 167.85 RR calculated by review [34]	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[40] Controlled clinical trial	13 people with episodic cluster headache 10 to 15 days into a cluster bout In review [28] [34]	**Adverse effects** with HBOT with placebo See further information on studies for full details on treatments The controlled clinical trial reported no adverse effects			

Further information on studies

[40] People receiving HBOT were placed into a hyperbaric chamber 5 minutes after onset of the attack, and the pressure was gradually increased to 2.0 atmosphere absolute for 30 minutes. People receiving placebo were placed in the same environment without receiving HBOT. The mean duration of the last three attacks occurring before the trial was calculated and compared with the duration of the attacks occurring during the intervention phase. The RCT did not carry out a between group statistical assessment. However, it found that HBOT, but not placebo, significantly reduced the duration of cluster headache attacks compared with baseline (absolute numbers not reported; P <0.01 for HBOT).

Comment: **Clinical guide:**
It is difficult to comment on the efficacy of HBOT, given the limited controlled data available in the literature. However, it is noteworthy that the available data point towards a beneficial effect — which is not surprising considering the beneficial effect of normobaric oxygen. HBOT has been associated with adverse effects, including: damage to the ears, sinuses, and lungs from the effects of pressure; temporary worsening of short-sightedness; claustrophobia; and oxygen poisoning. Although serious adverse effects are rare, HBOT cannot be regarded as an entirely benign intervention. [41] The clinical utility of HBOT is likely to remain limited in the foreseeable future, owing to the lack of general availability.

OPTION LIDOCAINE (INTRANASAL)

- For GRADE evaluation of interventions for Cluster headache, see table, p 38 .
- We don't know whether intranasal lidocaine, p 17 is effective for abortive treatment of cluster headache.

Benefits and harms

Lidocaine (intranasal):

We found no systematic review or RCTs.

Further information on studies

Comment: **Clinical guide:**
Small observational studies without a matched control group (the most recent published in 1995) found that intranasal lidocaine 4% spray or solution may be effective in at least one third of people. [42] [43] [44]

OPTION SUMATRIPTAN (ORAL) FOR ABORTING CLUSTER HEADACHE

- For GRADE evaluation of interventions for Cluster headache, see table, p 38 .
- We don't know whether oral sumatriptan, p 17 is effective as abortive treatment of episodic or chronic cluster headaches.

Benefits and harms

Sumatriptan (oral) for aborting cluster headache:

We found no systematic review or RCTs of oral sumatriptan for the abortive treatment of episodic or chronic cluster headache.

Further information on studies

Comment: None.

QUESTION What are the effects of interventions to prevent cluster headache?

OPTION GREATER OCCIPITAL NERVE INJECTIONS (BETAMETHASONE PLUS XYLOCAINE)

- For GRADE evaluation of interventions for Cluster headache, see table, p 38 .
- There is consensus that greater occipital nerve injections are effective for the prevention of episodic or chronic cluster headaches.

Benefits and harms

Single greater occipital nerve injection versus placebo:

We found no systematic review. We found one RCT comparing ipsilateral greater occipital nerve injection versus placebo. [45]

Headache relief

Greater occipital nerve injections compared with placebo Greater occipital nerve injections of betamethasone plus xylocaine may be more effective at reducing the frequency of attacks in the short term in people with episodic or cluster headaches (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Headache relief					
[45] RCT	23 people; 16 (70%) with episodic cluster headache, 7 (30%) with chronic cluster headache	**Attack free , 1 week** 11/13 (85%) with ipsilateral greater occipital nerve injection 0/10 (0%) with placebo In the intervention group, people were injected with 2.0 mL betamethasone dipropionate 12.46 mg plus disodium phosphate 5.26 mg plus 0.5 mL xylocaine 2% Placebo injection was 2.0 mL physiological saline plus 0.5 mL xylocaine 2%	P = 0.0001	○○○	betamethasone
[45] RCT	23 people; 16 (70%0 with episodic cluster headache, 7 (30%) with chronic cluster headache	**Attack free within 72 hours , 4 weeks** 8/13 (61%) with ipsilateral greater occipital nerve injection 0/10 (0%) with placebo 5/9 (56%) people with ECH and 3/4 (75%) people with CCH were attack free with betamethasone See further information on studies for details of rate of return of cluster headache In the intervention group, people were injected with 2.0 mL betamethasone dipropionate 12.46 mg plus disodium phosphate 5.26 mg plus 0.5 mL xylocaine 2% Placebo injection was 2.0 mL physiological saline plus 0.5 mL xylocaine 2%	P = 0.0026	○○○	betamethasone

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[45] RCT	23 people; 16 (70%) with episodic cluster headache, 7 (30%) with chronic cluster headache	**Adverse effects** with ipsilateral greater occipital nerve injection with placebo The RCT reported that two people who were given betamethasone injection had transient pain at the injection site In the intervention group, people were injected with 2.0 mL betamethasone dipropionate 12.46 mg plus disodium phosphate 5.26 mg plus 0.5 mL xylocaine 2% Placebo injection was 2.0 mL physiological saline plus 0.5 mL xylocaine 2%			

Further information on studies

[45] Cluster headache attacks resumed within 2 months after completion of the trial in 3/8 (38%) responders, whereas 5/8 (62%) responders (one person with chronic cluster headache) remained attack free for 4 to 26 months. People with episodic cluster headache were included only if the typical duration of their cluster bout was at least 4 weeks, and if they had been in a new bout for no longer than 1 week. All participants continued their usual acute treatment, and also continued other preventive treatment if the dose of preventive medication had been stable for 2 weeks.

Comment: **Clinical guide:**
There is consensus based on observational evidence that greater occipital nerve injections are effective for the prevention of episodic or chronic cluster headache. [37]

OPTION CORTICOSTEROIDS (ORAL)

- For GRADE evaluation of interventions for Cluster headache, see table, p 38 .
- There is consensus that corticosteroids, p 19 are effective for the prevention of episodic or chronic cluster headache.

Benefits and harms

Corticosteroids versus placebo:

We found one systematic review (search date 1998), [28] which identified one small crossover RCT. [46] The RCT compared prednisolone versus placebo for 15 months. We found no RCTs of corticosteroids other than prednisolone in people with cluster headache.

Headache relief

Prednisolone compared with placebo Prednisolone may be more effective at reducing the frequency of cluster headache attacks (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Headache relief					
[46] RCT **Crossover design**	19 people with cluster headache unresponsive to various drugs, including methysergide and ergotamine In review [28] See further information on studies for definition of cluster headache	**Pain free , 10 days** 17/19 (89%) with prednisolone 20 mg every alternate day with placebo absolute numbers for placebo not reported	P = 0.03 See further information on studies for methodological issues	○○○	prednisolone

Adverse effects

No data from the following reference on this outcome. [46]

Further information on studies

[46] Cluster headache was defined using the classification criteria provided by Kunkle and colleagues [47] and Bickerstaff, [48] as the trial pre-dated the International Headache Society classification criteria. **Methodological issues:** The RCT gave no information about the details of crossover, no washout period was reported, and it was unclear whether results were reported before or after crossover. There were also insufficient data about outcomes, and absolute figures and significance values were unclear. Because of these methodological issues, no conclusions can be drawn from this RCT.

Comment:

One retrospective study of prednisolone (10–80 mg/day) in 19 people (9 with episodic cluster headache; 10 with chronic cluster headache) reported greater than 50% relief in 73% of people, and complete relief in 58%. [49] Recurrence of headaches was reported in 79% of people when the prednisolone dose was tapered. Another observational study reported that, of 77 people with episodic cluster headache unresponsive to methysergide, prednisolone relieved 77% and partially improved 12%. [11] Prednisolone was also found to provide marked relief in 40% of people with chronic cluster headache, and was more effective than methysergide in this group. Headache relief was not defined in either study.

Clinical guide:

There is consensus based on observational evidence that corticosteroids are effective for the prevention of episodic and chronic cluster headache. [37] Corticosteroids are usually used as an initial treatment in conjunction with other preventive interventions such as verapamil and lithium, which have a slower onset of action, until verapamil and lithium are effective. An alternative strategy is to withhold corticosteroids in reserve until the patient is at the peak of the cluster bout, in case the alternative preventive strategy implemented is ineffective. In some European countries, prednisolone has been discontinued. In countries where prednisolone in not available, prednisone is used, with response rates comparable to those reported for prednisolone. [50] Systemic corticosteroids can cause the same adverse effects when used for cluster headache as in other diseases. The shortest course of prednisolone and dexamethasone reported to be associated with osteonecrosis of the femoral head is a 30-day course for prednisolone and a 7-day course for dexamethasone. [51] It is therefore prudent to restrict the duration of the courses of corticosteroids to these limits, and to consider limiting each patient to twice-yearly courses of treatment.

OPTION LITHIUM (ORAL)

- For GRADE evaluation of interventions for Cluster headache, see table, p 38 .
- We found no direct information from RCTs about whether lithium, p 21 is better than no active treatment for the prevention of cluster headache. There is current consensus that lithium, although commonly used and believed to be effective, is less effective than verapamil and causes more adverse effects.

Benefits and harms

Lithium versus placebo:

We found one systematic review (search date 1998), which identified no RCTs of sufficient quality. [28] The searches in the review were restricted to English language studies. We found no subsequent RCTs comparing lithium versus placebo for the prevention of cluster headache.

Lithium versus verapamil:

See option on verapamil, p 21 .

Further information on studies

Comment:

Clinical guide:

A non-systematic review of case reports and case series (all conducted in the 1970s) suggested that lithium may be an effective preventive treatment for cluster headache, but found that the response was less robust in episodic than in chronic cluster headache. [52] Collectively, in over 28 clinical trials involving 468 people, good results were reported in 236/304 (78%) people with chronic cluster headache and in 103/164 (63%) people with episodic cluster headache. [52] There is current consensus based on observational evidence that lithium, although commonly used and believed to be effective, is less effective than verapamil and causes more adverse effects. [37]

OPTION VERAPAMIL

- For GRADE evaluation of interventions for Cluster headache, see table, p 38 .
- There is consensus that verapamil, p 21 is more effective and has fewer adverse effects than lithium when used in prevention of chronic cluster headaches.

Benefits and harms

Verapamil versus placebo:

We found one systematic review (search date 1998), which identified no RCTs comparing verapamil versus placebo. [28] The searches in the systematic review were restricted to English language studies. We found one subsequent RCT. [53]

Headache relief

Verapamil compared with placebo Verapamil may be more effective at reducing the frequency of attacks at 2 weeks in people with episodic cluster headaches (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Headache frequency					
[53] RCT	30 people with episodic cluster headache	**Reduction in headache frequency >50% , 2 weeks** 12/15 (80%) with verapamil 360 mg daily	Significance not assessed Method of randomisation was unclear		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		0/15 (0%) with placebo			
Mean number of attacks					
[53] RCT	30 people with episodic cluster headache	**Mean number of attacks , first week** 1.1 with verapamil 360 mg daily 1.7 with placebo	Significance not assessed Method of randomisation was unclear		
[53] RCT	30 people with episodic cluster headache	**Mean number of attacks , second week** 0.6 with verapamil 360 mg daily 1.65 with placebo	P <0.001 Method of randomisation was unclear	○○○	verapamil

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[53] RCT	30 people with episodic cluster headache	**Constipation** 8/15 (53%) with verapamil 360 mg daily 0/15 (0%) with placebo	Significance not assessed Method of randomisation was unclear		
[53] RCT	30 people with episodic cluster headache	**Mean decrease in blood pressure after treatment** 11 mm Hg with verapamil 360 mg daily 2 mm Hg with placebo There were no reported symptoms of postural hypotension	P <0.05 Method of randomisation was unclear	○○○	placebo
[53] RCT	30 people with episodic cluster headache	**Mean decrease in heart rate after treatment** 10 bpm with verapamil 360 mg daily 1 bpm with placebo	P <0.05 Method of randomisation was unclear	○○○	placebo

Verapamil versus lithium:

We found one systematic review (search date 1998), [28] which identified one RCT (30 people with chronic cluster headache, crossover design) comparing verapamil 360 mg daily versus lithium carbonate 900 mg daily, each given for 8 weeks. [54] The RCT did not compare verapamil versus lithium directly. Instead, it reported changes in both groups from baseline. We therefore have not reported results from this RCT. [54]

Further information on studies

Comment: **Clinical guide:**
In clinical practice, verapamil at doses of up to 960 mg daily is often used for the prevention of cluster headache, with anecdotal success in those with poor response at lower doses. There is consensus based on observational evidence that verapamil is more effective than lithium and causes fewer adverse effects. [37] It is important when using verapamil to closely monitor the ECG for changes suggestive of heart block (prolongation of PR interval, change in cardiac axis, or broadening of QRS complex). Serial ECGs are recommended during dose titration, and should probably be monitored in the long term, because PR prolongation can develop during maintenance treatment. [55] [56]

OPTION BACLOFEN (ORAL)

- For GRADE evaluation of interventions for Cluster headache, see table, p 38 .
- We found no direct information from RCTs about the effects of baclofen, p 23 for prevention of cluster headaches. However, baclofen is not routinely used for cluster headache prophylaxis.

Benefits and harms

Baclofen (oral):

We found no systematic review or RCTs.

Further information on studies

Comment: **Clinical guide:**
Baclofen is not routinely used for cluster headache prophylaxis.

OPTION BOTULINUM TOXIN (INTRAMUSCULAR)

- For GRADE evaluation of interventions for Cluster headache, see table, p 38 .
- We found no direct information from RCTs about the effects of botulinum toxin, p 23 for prevention of cluster headaches. However, botulinum toxin is not routinely used for cluster headache prophylaxis.

Benefits and harms

Botulinum toxin (intramuscular):

We found one systematic review (search date 2003), which identified no RCTs. [57] We found no subsequent RCTs.

Further information on studies

Comment: **Clinical guide:**
Botulinum toxin is not routinely used for cluster headache prophylaxis.

OPTION CAPSAICIN (INTRANASAL)

- For GRADE evaluation of interventions for Cluster headache, see table, p 38 .
- We don't know whether capsaicin, p 23 is effective for prevention of cluster headache. We found no direct information about the effects of capsaicin in people with chronic cluster headaches.
- Capsaicin is associated with transient adverse effects, such as burning sensations, lacrimation, and rhinorrhoea.

Benefits and harms

Ipsilateral versus contralateral capsaicin:

We found one systematic review (search date 1998), [28] which identified one RCT. [58] The searches in the systematic review were restricted to English language studies.

Headache relief

Ipsilateral compared with contralateral capsaicin Applying capsaicin ipsilaterally may be more effective at reducing the frequency of attacks of episodic cluster headache (very low-quality evidence)

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Frequency of attacks					
[58] RCT	51 people with episodic cluster headache In review [28]	**Number of attacks per 10-day period after treatment , first to third 10-day period** with ipsilateral intranasal capsaicin (300 micrograms) with contralateral intranasal capsaicin (300 micrograms) Absolute results reported graphically Capsaicin was started at least 15 days after the beginning of the cluster period, and applied once daily for 5 to 8 days	P <0.01 See further information on studies for methodological issues	○○○	ipsilateral intranasal capsaicin
[58] RCT	51 people with episodic cluster headache In review [28]	**Number of attacks per 10-day period after treatment , fourth and fifth 10-day period** with ipsilateral intranasal capsaicin (300 micrograms) with contralateral intranasal capsaicin (300 micrograms) Absolute results reported graphically Capsaicin was started at least 15 days after the beginning of the cluster period, and applied once daily for 5 to 8 days	P <0.05 See further information on studies for methodological issues	○○○	ipsilateral intranasal capsaicin
[58] RCT	51 people with episodic cluster headache In review [28]	**Greater than 50% reduction in the number of attacks** 8/26 (31%) with ipsilateral intranasal capsaicin (300 micrograms) 0/25 (0%) with contralateral intranasal capsaicin (300 micrograms) Capsaicin was started at least 15 days after the beginning of the cluster period, and applied once daily for 5 to 8 days	Significance not assessed See further information on studies for methodological issues		

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[58] RCT	51 people with episodic cluster headache In review [28]	**Adverse effects** with ipsilateral intranasal capsaicin (300 micrograms) with contralateral intranasal capsaicin (300 micrograms) The RCT reported that an intense burning sensation and rhinorrhoea were present in all participants during the first application of intranasal capsaicin. The burning sensation decreased with further applications, and disappeared after five to eight applications No other adverse effects were reported Capsaicin was started at least 15 days after the beginning of the cluster period, and applied once daily for 5 to 8 days	See further information on studies for methodological issues		

Further information on studies

[58] Thirteen of 26 (50%) people given ipsilateral capsaicin were rendered pain free for the remainder of the trial. The method of randomisation was not specified. Participants in the RCT were told that they might be receiving an alternative treatment, the effect of which could not be predicted. The authors assert that this approach approximated a single-blind study design.

Comment: Intranasal capsaicin produces an intense burning sensation, lacrimation, and rhinorrhoea that lasts for about 20 minutes, although these symptoms progressively decrease and disappear after five to eight applications. Because of this irritant local effect, it is difficult to conduct double-blind studies of intranasal capsaicin.

OPTION CHLORPROMAZINE

- For GRADE evaluation of interventions for Cluster headache, see table, p 38 .
- We found no direct information from RCTs about chlorpromazine, p 25 for the prevention of cluster headache. Chlorpromazine is not routinely used in clinical practice because it can be associated with severe adverse effects.

Benefits and harms

Chlorpromazine:

We found no systematic review or RCTs.

Comment: **Clinical guide:**
Chlorpromazine is not routinely used in clinical practice for cluster headache prophylaxis. Furthermore, its use needs to be balanced against the potential adverse effects. Tardive dyskinesia can be permanent even after a few doses. Dystonic reactions and akathisia can occur, occasionally developing into a severe sense of restlessness or agitation. Drowsiness occurs in many people.

OPTION CIVAMIDE (INTRANASAL)

- For GRADE evaluation of interventions for Cluster headache, see table, p 38 .
- We don't know whether intranasal civamide, p 26 is more effective than placebo at preventing the frequency, intensity, and number of severe headaches in people with episodic cluster headaches. We found no direct information from RCTs assessing civamide in people with chronic cluster headache.
- Civamide has been associated with nasal burning sensations and lacrimation.

Benefits and harms

Civamide (intranasal) versus placebo:

We found no systematic review. We found one RCT in people with episodic cluster headache. [59] We found no RCTs of civamide in people with chronic cluster headache.

Headache relief

Intranasal civamide compared with placebo We don't know whether intranasal civamide is more effective than placebo at preventing the frequency, intensity, and number of severe headaches in people with episodic cluster headaches (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Headache frequency					
[59] RCT	28 people with episodic cluster headache	**Decrease from baseline , 1 to 7 days after treatment completed** –55.5% (absolute number of headaches a week decreased from 12.5 to 5.6) with civamide (100 microlitres of 0.025% solution) –25.9% (absolute number of headaches a week decreased from 10.8 to 7.3) with placebo (100 microlitres of the vehicle)	P value for % decrease = 0.03 See further information on studies for methodological issues	○○○	civamide
[59] RCT	28 people with episodic cluster headache	**Decrease from baseline , 8 to 14 days after treatment completed** –66.9% (absolute number of headaches a week decreased from 12.5 to 4.1) with civamide (100 microlitres of 0.025% solution) –32.3% (absolute number of headaches a week decreased from 10.8 to 7.2) with placebo (100 microlitres of the vehicle)	P value for decrease in number of headaches = 0.09 P value for % decrease = 0.07 See further information on studies for methodological issues	⟷	Not significant
[59] RCT	28 people with episodic cluster headache	**Decrease from baseline , 14 to 18 days after treatment completed** –70.6% (absolute number of headaches a week decreased from 12.5 to 4.2) with civamide (100 microlitres of 0.025% solution) –34.7% (absolute number of headaches a week decreased from 10.8 to 7.2) with placebo (100 microlitres of the vehicle)	P value for decrease in the number of headaches = 0.07 P value for % decrease = 0.07 See further information on studies for methodological issues	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[59] RCT	28 people with episodic cluster headache	**Decrease from baseline , 1 to 20 days after treatment completed** –61.4% (absolute number of headaches a week decreased from 12.5 to 4.9) with civamide (100 microlitres of 0.025% solution) –30.9% (absolute number of headaches a week decreased from 10.8 to 7.2) with placebo (100 microlitres of the vehicle)	P value for % decrease = 0.054 The difference was of borderline significance See further information on studies for methodological issues	⟷	Not significant favour should be blank
[59] RCT	28 people with episodic cluster headache	**Number of severe headaches** with civamide (100 microlitres of 0.025% solution) with placebo (100 microlitres of the vehicle) Absolute results not reported	Reported as not significant P value not reported See further information on studies for methodological issues	⟷	Not significant
Pain severity					
[59] RCT	28 people with episodic cluster headache	**Cluster headache pain intensity** with civamide (100 microlitres of 0.025% solution) with placebo (100 microlitres of the vehicle) Absolute results not reported	Reported as not significant P value not reported See further information on studies for methodological issues	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Nasal burning					
[59] RCT	28 people with episodic cluster headache	**Nasal burning** 14/18 (78%) with civamide (100 microlitres of 0.025% solution) 1/10 (10%) with placebo (100 microlitres of the vehicle)	P = 0.001 See further information on studies for methodological issues	○○○	placebo
Lacrimation					
[59] RCT	28 people with episodic cluster headache	**Lacrimation** 9/18 (50%) with civamide (100 microlitres of 0.025% solution) 0/10 (0%) with placebo (100 microlitres of the vehicle)	P = 0.01 See further information on studies for methodological issues	○○○	placebo

Further information on studies

[59] The RCT was randomised in a ratio of two civamide (18 people) to one placebo (10 people). Only people who received at least 3 days of treatment were included in the analysis. Although the authors report that this RCT was double blind, the irritant nature of nasally applied civamide is likely to have led to unblinding.

Comment: **Clinical guide:**
Intranasal civamide is not routinely used in clinical practice for cluster headache prophylaxis.

OPTION CLONIDINE (TRANSDERMAL)

- For GRADE evaluation of interventions for Cluster headache, see table, p 38 .
- We found no direct information from RCTs about transdermal clonidine, p 28 for the prevention of cluster headache.

Benefits and harms

Clonidine (transdermal):

We found no systematic review or RCTs.

Further information on studies

Comment: None.

OPTION ERGOTAMINE AND DIHYDROERGOTAMINE (ORAL OR INTRANASAL)

- For GRADE evaluation of interventions for Cluster headache, see table, p 38 .
- We don't know whether ergotamine or dihydroergotamine, p 28 are effective for prevention of cluster headache as we found no direct information from RCTs.

Benefits and harms

Ergotamine and dihydroergotamine (oral or intranasal):

We found one systematic review (1998), which identified no RCTs. [28] The searches in the systematic review were restricted to English language studies. We found no subsequent RCTs.

Further information on studies

Comment: **Clinical guide:**
Oral ergotamine was first reported to be effective as a preventive treatment in 81% of people with cluster headache in a case series published in 1947. [60] In 1956, it was reported in a case series that a rectal suppository of ergotamine plus caffeine or intramuscular ergotamine injections at bedtime were effective in preventing nocturnal attacks. [61] Ergotamine was routinely recommended for the prevention of cluster headache until the efficacy of verapamil and lithium became evident. It is now rarely used in clinical practice. Additionally, a retrospective cohort study found that repetitive intravenous dihydroergotamine given in hospital over 3 days was useful in the abortive treatment

of cluster headache. [62] Ergot derivatives should not be combined or used with methysergide and triptans.

OPTION GABAPENTIN (ORAL)

- For GRADE evaluation of interventions for Cluster headache, see table, p 38 .
- We don't know whether gabapentin, p 29 is effective for prevention of cluster headache as we found no direct information from RCTs.

Benefits and harms

Gabapentin (oral):

We found no systematic review or RCTs.

Further information on studies

Comment:

We found one small observational study assessing gabapentin 900 mg daily in 12 people (8 people with episodic cluster headache; 4 with chronic cluster headache), which found that all participants were rendered pain free within 8 days. [63] People with episodic cluster headache discontinued gabapentin after 60 days of treatment without recurrence of the attacks. The four people with chronic cluster headache remained pain free at 4-month follow-up. This high response rate needs to be reproduced in controlled trials.

Clinical guide:
In clinical practice, specialists use gabapentin for cluster headache prophylaxis when patients have failed trials of preventive agents routinely used, such as verapamil, lithium, and corticosteroids.

OPTION LEUPROLIDE

- For GRADE evaluation of interventions for Cluster headache, see table, p 38 .
- We don't know whether leuprolide, p 29 is effective for prevention of cluster headache as we found no direct information from RCTs.

Benefits and harms

Leuprolide:

We found one systematic review (search date 1998), [28] which identified one RCT. [64] The searches in the systematic review were restricted to English language studies. The RCT (60 men with chronic cluster headache) compared a single dose of intramuscular leuprolide (a synthetic slow-release GnRH analogue) versus placebo. [64] The RCT did not compare leuprolide versus placebo directly. Instead, it reported changes in both groups from baseline. We therefore have not reported results from this RCT. We found no RCTs on the effects of leuprolide for episodic cluster headache. The RCT reported that leuprolide significantly decreased libido compared with baseline (significance figures not reported). [64]

Further information on studies

Comment:

Clinical guide:
Leuprolide is rarely used in clinical practice for cluster headache prophylaxis.

OPTION MELATONIN

- For GRADE evaluation of interventions for Cluster headache, see table, p 38 .
- We don't know whether melatonin, p 30 is effective for prevention of cluster headache as we found no direct information from RCTs.

Benefits and harms

Melatonin:

We found one systematic review (search date 1998), [28] which identified one RCT. [65] The RCT (20 people; 18 with episodic cluster headache; 2 with chronic cluster headache) compared oral melatonin 10 mg daily versus placebo for 2 weeks. The RCT did not compare melatonin versus placebo directly. Instead, it reported changes in both groups from baseline. We have therefore not reported results from this RCT. [65] The RCT reported no adverse effects associated with melatonin. [65]

Further information on studies

Comment: **Clinical guide:**
Melatonin is not routinely used in cluster headache prophylaxis.

OPTION METHYSERGIDE (ORAL)

- For GRADE evaluation of interventions for Cluster headache, see table, p 38 .
- We don't know whether methysergide, p 30 is effective for prevention of cluster headache as we found no direct information from RCTs.

Benefits and harms

Methysergide (oral):

We found one systematic review (search date 1998), which identified no RCTs. [28] The searches in the systematic review were restricted to English language studies. We found no subsequent RCTs.

Further information on studies

Comment: **Clinical guide:**
A narrative review of observational studies published in 1967, most with no matched controls, found that methysergide was an effective preventive drug for people with cluster headache. [66] It reported that methysergide 3 mg to 12 mg daily was effective in 73% of people with episodic cluster headache and chronic cluster headache. A subsequent observational study found that methysergide was effective in 65% of people with episodic cluster headache and in 20% with chronic cluster headache, but that in up to 20% of people it seemed to lose effectiveness with repeated use. [11] Study design and duration were not reported. Another prospective cohort study of methysergide 3 mg to 12 mg daily in people with episodic and chronic cluster headache found a beneficial preventive effect in 31% of people, with no difference in treatment response between the episodic and chronic groups. [67] In addition, a retrospective analysis of 164 people with cluster headache (type not specified) found a satisfactory response in only 26% of people. [67] Hence, the efficacy data on methysergide from observational studies seem to suggest that it is effective, albeit that the data are inconsistent. Prolonged treatment with methysergide has been associated with fibrotic reactions (retroperitoneal, pulmonary, pleural, and cardiac) although these are rare. [68] Ideally, methysergide should be used in people with short cluster bouts, preferably for less than 3 to 4 months. If prolonged use is intended,

then the risk of fibrotic reactions can be minimised by giving methysergide for 6 months followed by a 1-month drug holiday, before restarting methysergide. Some clinicians use prolonged methysergide with careful monitoring, which includes auscultation of the heart and yearly echocardiogram, chest x ray, and abdominal magnetic resonance imaging. [69] All people receiving methysergide should remain under the supervision of the treating physician, and should be examined regularly for the development of visceral fibrosis or vascular complications.

OPTION PIZOTIFEN (ORAL)

- For GRADE evaluation of interventions for Cluster headache, see table, p 38 .
- We don't know whether pizotifen, p 31 is effective for prevention of cluster headache as we found no direct information from RCTs.

Benefits and harms

Pizotifen (oral):

We found one systematic review (search date 1998), which identified no RCTs. [28] The searches in the systematic review were restricted to English language studies. We found no subsequent RCTs.

Further information on studies

Comment: One small, single-blind, non-randomised, crossover-design controlled trial (28 people with episodic cluster headache) found that pizotifen significantly reduced the "headache index" — a composite score of headache attack, duration, and severity — compared with placebo. [70] Adverse effects of pizotifen included drowsiness, nausea, anxiety, and increased weight. This non-RCT has various methodological flaws that probably contribute to an overestimation of the effectiveness of pizotifen. All participants were given placebo first followed by pizotifen, and therefore the improvement in some people while taking pizotifen probably represents natural history of the cluster bout. Furthermore, the single-blind design may also have introduced bias. A review of seven small observational studies reported that pizotifen had only a modest effect in cluster headache prophylaxis — being effective in 38% of people with cluster headache. [71]

OPTION SODIUM VALPROATE (ORAL)

- For GRADE evaluation of interventions for Cluster headache, see table, p 38 .
- We don't know whether sodium valproate, p 31 is effective for prevention of cluster headache.

Benefits and harms

Sodium valproate (oral) versus placebo:

We found two systematic reviews (search dates 1998 [28] and not reported). [72] The first review identified no RCTs. [28] The second review identified one RCT comparing sodium valproate versus placebo for 2 weeks. [73]

Headache relief

Sodium valproate compared with placebo We don't know whether sodium valproate is more effective than placebo for prophylaxis of cluster headaches (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Headache frequency					
[73] RCT	96 people, 73 with ECH and 17 with CCH In review [72]	**Proportion of people with >50% reduction in the average number of attacks , 2 weeks** 50% with sodium valproate (1000 mg to 2000 mg daily)	P = 0.23 See further information on studies for methodological issues	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		62% with placebo Absolute numbers not reported			

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[73] RCT	96 people, 73 with ECH and 17 with CCH In review [72]	**Adverse effects** 40% with sodium valproate (1000 mg to 2000 mg daily) 28% with placebo Absolute numbers not reported The RCT did not report any serious adverse effects	Significance not assessed See further information on studies for methodological issues		
Nausea and vomiting					
[73] RCT	96 people, 73 with ECH and 17 with CCH In review [72]	**Nausea and vomiting** 12% with sodium valproate (1000 mg to 2000 mg daily) 4% with placebo Absolute numbers not reported Nausea and vomiting reported to be one of the most common adverse effects	Significance not assessed See further information on studies for methodological issues		
Somnolence					
[73] RCT	96 people, 73 with ECH and 17 with CCH In review [72]	**Somnolence** 12% with sodium valproate (1000 to 2000 mg daily) 2% with placebo Absolute numbers not reported Somnolence reported to be one of the most common adverse effects	Significance not assessed See further information on studies for methodological issues		

Further information on studies

[73] The results may have been affected by the mean duration of previous cluster bouts at baseline in people with episodic cluster headache being shorter in the placebo group than in the intervention group, although the difference between groups was not significant (78.3 days with sodium valproate *v* 62.4 days with placebo; reported as not significant; P value not reported). Consequently, the high response rate in the placebo group may be attributable to the spontaneous remission of the cluster bout in addition to a true placebo response. Because of these weaknesses in trial methods, the authors of the review reported that no conclusions could be drawn about the effectiveness of sodium valproate for the prophylaxis of cluster headache.

Comment: None.

OPTION SUMATRIPTAN (ORAL) FOR PREVENTING CLUSTER HEADACHE

- For GRADE evaluation of interventions for Cluster headache, see table, p 38 .
- We don't know whether oral sumatriptan is effective for prevention of cluster headache.

Benefits and harms

Sumatriptan (oral) versus placebo:

We found one systematic review (search date 1998), [28] which identified one RCT. [74]

Headache relief

Oral sumatriptan compared with placebo Oral sumatriptan seems no more effective than placebo at preventing attacks of episodic or cluster headaches (moderate-quality evidence)

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Headache frequency					
[74] RCT	169 people; 90 (53%) with episodic cluster headache, 78 (47%) with chronic cluster headache In review [28]	**At least 50% reduction in number of attacks from observation week to study treatment week** 20/89 (23%) with sumatriptan (100 mg three times a day) 17/79 (22%) with placebo See further information on studies for details on treatment regimen and assessment of headache severity	P = 0.88	⟷	Not significant
[74] RCT	169 people; 90 (53%) with episodic cluster headache, 78 (47%) with chronic cluster headache In review [28]	**At least 50% reduction in number of severe/very severe attacks from observation week to study treatment week** 32/74 (43%) with sumatriptan (100 mg three times a day) 27/64 (42%) with placebo See further information on studies for details on treatment regimen and assessment of headache severity	P = 0.84	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[74] RCT	169 people; 90 (53%) with episodic cluster headache, 78 (47%) with chronic cluster headache In review [28]	**Adverse effects** 31/89 (35%) with sumatriptan (100 mg three times a day) 19/79 (24%) with placebo Adverse effects reported included nausea and vomiting, headache, and malaise/fatigue See further information on studies for other details on adverse effects	Significance not assessed		

Further information on studies

[74] People were initially observed for 1 week, and those experiencing a minimum of seven attacks entered the intervention stage of the trial. All participants were initially treated with a subcutaneous injection of sumatriptan 6 mg, and were then randomised to receive either oral sumatriptan or placebo. Headache severity was assessed using a 5-point scale, ranging from 0 (no pain) to 4 (very severe pain). **Adverse effects** The RCT found that one person treated with sumatriptan developed cardiac flutter and chest pain, and a second person reported numbness and pressure in the chest with shortness of breath. A third person developed pericarditis, which was thought unlikely to be drug related.

Comment: **Clinical guide:**
There is some consensus among neurologists that oral sumatriptan has no place in the preventive management of cluster headache, as it is ineffective.

OPTION TOPIRAMATE (ORAL)

- For GRADE evaluation of interventions for Cluster headache, see table, p 38 .
- We don't know whether topiramate, p 34 is effective for prevention of cluster headache.

Benefits and harms

Topiramate (oral):

We found no systematic review or RCTs.

Further information on studies

Comment: **Clinical guide:**
Observational studies without matched control groups have found that topiramate may be effective for prophylaxis of cluster headache in about 50% of people. [75] [76] [77] [78] [79] In clinical practice, topiramate is used for cluster headache prophylaxis when patients have failed trials of routinely used preventive agents such as verapamil, lithium, and corticosteroids.

OPTION TRICYCLIC ANTIDEPRESSANTS

- For GRADE evaluation of interventions for Cluster headache, see table, p 38 .
- We don't know whether tricyclic antidepressants, p 34 are effective for prevention of cluster headache.

Benefits and harms

Tricyclic antidepressants:

We found no systematic review or RCTs.

Further information on studies

Comment: **Clinical guide:**
There is some consensus among neurologists that tricyclic antidepressants have no place in the preventive management of cluster headache, as they are ineffective.

GLOSSARY

Low-quality evidence 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.

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

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Zolmitriptan (intranasal) to abort cluster headache New option for which we found two RCTs. [32] [33] Both RCTs found that intranasal zolmitriptan improved headache relief and pain at 30 minutes compared with placebo. Categorised as Beneficial.

High-dose and high-flow-rate oxygen One systematic review added identified no new evidence assessing the effects of high-dose and high-flow-rate oxygen to abort cluster headache. [34] Categorisation unchanged (Likely to be beneficial by consensus).

Hyperbaric oxygen One systematic review added identified no new evidence assessing the effects of hyperbaric oxygen to abort cluster headache. [34] Categorisation unchanged (Unknown effectiveness).

REFERENCES

1. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 2nd ed. *Cephalalgia* 2004;24 (supplement 1):9–160.
2. Ekbom K, Ahlborg B, Schele R. Prevalence of migraine and cluster headache in Swedish men of 18. *Headache* 1978;18:9–19.[PubMed]
3. D'Alessandro R, Gamberini G, Benassi G, et al. Cluster headache in the Republic of San Marino. *Cephalalgia* 1986;6:159–162.[PubMed]
4. Swanson JW, Yanagihara T, Stang PE, et al. Incidence of cluster headaches: a population-based study in Olmsted County, Minnesota. *Neurology* 1994;44:433–437.[PubMed]
5. Tonon C, Guttmann S, Volpinin M, et al. Prevalence and incidence of cluster headache in the Republic of San Marino. *Neurology* 2002;58:1407–1409.[PubMed]
6. Sjaastad O, Bakketeig LS. Cluster headache prevalence. Vaga study of headache epidemiology. *Cephalalgia* 2003;23:528–533.[PubMed]
7. Torelli P, Beghi E, Manzoni GC. Cluster headache prevalence in the Italian general population. *Neurology* 2005;64:469–474.[PubMed]
8. Russell MB. Epidemiology and genetics of cluster headache. *Lancet Neurol* 2004;3:279–283.[PubMed]
9. Horton BT. Histaminic cephalgia: differential diagnosis and treatment. *Proc Staff Meet Mayo Clin* 1956;31:325–333.[PubMed]
10. Lovshin LL. Clinical caprices of histaminic cephalalgia. *Headache* 1961;1:7–10.[PubMed]
11. Kudrow L. Cluster headache: mechanisms and management. New York: Oxford University Press, 1980.
12. Ekbom K, Waldenlind E. Cluster headache in women: evidence of hypofertility(?) Headaches in relation to menstruation and pregnancy. *Cephalalgia* 1981;1:167–174.[PubMed]
13. Krabbe AA. Cluster headache: a review. *Acta Neurol Scand* 1986;74:1–9.[PubMed]
14. Klapper JA, Klapper A, Voss T. The misdiagnosis of cluster headache: a nonclinic, population-based, Internet survey. *Headache* 2000;40:730–735.[PubMed]
15. Torelli P, Cologno D, Cademartiri C, et al. Application of the International Headache Society classification criteria in 652 cluster headache patients. *Cephalalgia* 2001;21:145–150.[PubMed]
16. Bahra A, May A, Goadsby PJ. Cluster headache: a prospective clinical study with diagnostic implications. *Neurology* 2002;58:354–361.[PubMed]
17. Schurks M, Kurth T, de Jesus J, et al. Cluster headache: clinical presentation, lifestyle features, and medical treatment. *Headache* 2006;46:1246–1254.[PubMed]
18. Manzoni GC, Terzano MG. Bono G, et al. Cluster headache-clinical findings in 180 patients. *Cephalalgia* 1983;3:21–30.[PubMed]
19. Russell MB. Genetic epidemiology of migraine and cluster headache. *Cephalalgia* 1997;17:683–701.[PubMed]
20. Ekbom K. Patterns of cluster headache with a note on the relations to angina pectoris and peptic ulcer. *Acta Neurol Scand* 1970;46:225–237.[PubMed]
21. Manzoni GC. Gender ratio of cluster headache over the years: a possible role of changes in lifestyle. *Cephalalgia* 1998;18:138–142.[PubMed]
22. Kudrow L. Physical and personality characteristics in cluster headache. *Headache* 1974;13:197–202.[PubMed]
23. Manzoni GC. Cluster headache and lifestyle: remarks on a population of 374 male patients. *Cephalalgia* 1999;19:88–94.[PubMed]
24. Lance JW, Anthony M. Migrainous neuralgia or cluster headache? *J Neurol Sci* 1971;13:401–414.[PubMed]
25. Italian Cooperative Study Group on the Epidemiology of Cluster Headache (ICECH). Case-control study on the epidemiology of cluster headache. I: etiological factors and associated conditions. *Neuroepidemiology* 1995;14:123–127.[PubMed]
26. Manzoni GC, Micieli G, Granella F, et al. Cluster headache – course over ten years in 189 patients. *Cephalalgia* 1991;11:169–174.[PubMed]
27. Igarashi H, Sakai F. Natural history of cluster headache. *Cephalalgia* 1996;16:390–391.
28. Zakrzewska JM. Cluster headache: review of the literature. *Br J Oral Maxillofac Surg* 2001;39:103–113. Search date 1998.[PubMed]
29. The Sumatriptan Cluster Headache Study Group, Treatment of acute cluster headache with sumatriptan. *N Engl J Med* 1991;325:322–326.[PubMed]
30. Ekbom K, Monstad I, Prusinski A, et al. Subcutaneous sumatriptan in the acute treatment of cluster headache: a dose comparison study. The Sumatriptan Cluster Headache Study Group. *Acta Neurol Scand* 1993;88:63–69.[PubMed]
31. Van Vliet JA, Bahra A, Martin V, et al. Intranasal sumatriptan in cluster headache: randomized placebo-controlled double-blind study. *Neurology* 2003;60:630–633.[PubMed]
32. Cittadini E, May A, Straube A, et al. Effectiveness of intranasal zolmitriptan in acute cluster headache: a randomized, placebo-controlled, double-blind crossover study. *Arch Neurol* 2006;63:1537–1542.[PubMed]
33. Rapoport AM, Mathew NT, Silberstein SD, et al. Zolmitriptan nasal spray in the acute treatment of cluster headache: a double-blind study. *Neurology* 2007;69:821–826.[PubMed]
34. Bennett MH, French C, Schnabel A, et al. Normobaric and hyperbaric oxygen therapy for migraine and cluster headache. In: The Cochrane Library, Issue 2, 2009. Chichester, UK: John Wiley & Sons, Ltd. Search date 2008.[PubMed]
35. Fogan L. Treatment of cluster headache. A double-blind comparison of oxygen *v* air inhalation. *Arch Neurol* 1985;42:362–363.[PubMed]
36. Ad Hoc Committee on Classification of Headache. Classification of headache. *JAMA* 1962;179:717–718.
37. May A, Leone M, Afra J, et al. EFNS guidelines on the treatment of cluster headache and other trigeminal-autonomic cephalalgias. *Eur J Neurol* 2006;13:1066–1077.[PubMed]
38. Matharu MS, Levy, MJ, Meeran K, et al. Subcutaneous octreotide in cluster headache: randomized placebo-controlled double-blind crossover study. *Ann Neurol* 2004;56:488–494. [Erratum in *Ann Neurol* 2004;56:751][PubMed]
39. Bahra A, Gawel MJ, Hardebo JE, et al. Oral zolmitriptan is effective in the acute treatment of cluster headache. *Neurology* 2000;54:1832–1839.[PubMed]
40. Di Sabato F, Fusco BM, Pelaia P, et al. Hyperbaric oxygen therapy in cluster headache. *Pain* 1993;52:243–245.[PubMed]
41. Sheridan RL, Shank ES. Hyperbaric oxygen treatment: a brief overview of a controversial topic. *J Trauma* 1999;47:426–435.[PubMed]
42. Kittrelle JP, Grouse DS, Seybold ME. Cluster headache. Local anesthetic abortive agents. *Arch Neurol* 1985;42:496–498.[PubMed]
43. Hardebo JE, Elner A. Nerves and vessels in the pterygopalatine fossa and symptoms of cluster headache. *Headache* 1987;27:528–532.[PubMed]
44. Robbins L. Intranasal lidocaine for cluster headache. *Headache* 1995;35:83–84.[PubMed]
45. Ambrosini A, Vandenheede M, Rossi P, et al. Suboccipital injection with a mixture of rapid- and long-acting steroids in cluster headache: a double-blind placebo-controlled study. *Pain* 2005;118:92–96.[PubMed]
46. Jammes JL. The treatment of cluster headaches with prednisone. *Dis Nerv Syst* 1975;36:375–376.[PubMed]
47. Kunkle EC, Pfeiffer JB Jr, Wilhoit WM, et al. Recurrent brief headache in cluster pattern. *Trans Am Neurol Assoc* 1952;77:240–243.[PubMed]
48. Bickerstaff ER. Cluster headaches. In: Vinken PJ, Bruyn GW, eds. Handbook of clinical neurology. Amsterdam: Elsevier Science Publishers, 1968. 111–118.

49. Couch JR Jr, Ziegler DK. Prednisone therapy for cluster headache. *Headache* 1978;18:219–221.[PubMed]
50. Matharu MS, Boes CJ, Goadsby PJ. Management of trigeminal autonomic cephalgias and hemicrania continua. *Drugs* 2003;63:1637–1677.[PubMed]
51. Mirzai R, Chang C, Greenspan A, et al. The pathogenesis of osteonecrosis and the relationships to corticosteroids. *J Asthma* 1999;36:77–95.[PubMed]
52. Ekbom K. Lithium for cluster headache: review of the literature and preliminary results of long-term treatment. *Headache* 1981;21:132–139.[PubMed]
53. Leone M, D'Amico D, Frediani F, et al. Verapamil in the prophylaxis of episodic cluster headache: a double-blind study versus placebo. *Neurology* 2000;54:1382–1385.[PubMed]
54. Bussone G, Leone M, Peccarisi C, et al. Double blind comparison of lithium and verapamil in cluster headache prophylaxis. *Headache* 1990;30:411–417.[PubMed]
55. Cohen AS, Matharu MS, Goadsby PJ. EKG changes associated with the use of verapamil in cluster headache. *Neurology* 2006;66:A131.
56. Cohen AS, Matharu MS, Goadsby PJ. Electrocardiographic abnormalities in patients with cluster headache on verapamil therapy. *Neurology* 2007;69:668–675.[PubMed]
57. Sycha T, Kranz G, Auff E, et al. Botulinum toxin in the treatment of rare head and neck pain syndromes: a systematic review of the literature. *J Neurol* 2004;251:I19–I30. Search date 2003.[PubMed]
58. Fusco BM, Marabini S, Maggi CA, et al. Preventative effect of repeated nasal applications of capsaicin in cluster headache. *Pain* 1994;59:321–325.[PubMed]
59. Saper JR, Klapper J, Mathew NT, et al. Intranasal civamide for the treatment of episodic cluster headaches. *Arch Neurol* 2002;59:990–994.[PubMed]
60. Ekbom K. Ergotamine tartrate orally in Horton's 'histaminic cephalalgia' (also called Harris's 'ciliary neuralgia'). *Acta Psychiatr Neurol* 1947;46:106–113.
61. Symonds CP. A particular variety of headache. *Brain* 1956;79:217–232.[PubMed]
62. Mather PJ, Silberstein SD, Shulman EA, et al. The treatment of cluster headache with repetitive intravenous dihydroergotamine. *Headache* 1991;31:525–532.[PubMed]
63. Leandri M, Luzzani M, Cruccu G, et al. Drug-resistant cluster headache responding to gabapentin: a pilot study. *Cephalalgia* 2001;21:744–746.[PubMed]
64. Nicolodi M, Sicuteri F, Poggioni M. Hypothalamic modulation of nociception and reproduction in cluster headache. I. Therapeutic trials of leuprolide. *Cephalalgia* 1993;13:253–257.[PubMed]
65. Leone M, D'Amico D, Moschiano F, et al. Melatonin versus placebo in the prophylaxis of cluster headache: a double-blind pilot study with parallel groups. *Cephalalgia* 1996;16:494–496.[PubMed]
66. Curran DA, Hinterberger H, Lance JW. Methysergide. *Res Clin Stud Headache* 1967;1:74–122.
67. Krabbe A. Limited efficacy of methysergide in cluster headache. A clinical experience. *Cephalalgia* 1989;9:404–405.
68. Graham JR, Suby HI, LeCompte PR, et al. Fibrotic disorders associated with methysergide therapy for headache. *N Eng J Med* 1966;274:359–368.[PubMed]
69. Raskin NH. *Headache*. 2nd ed. New York: Churchill Livingstone, 1988.
70. Ekbom K. Prophylactic treatment of cluster headache with a new serotonin antagonist, BC 105. *Acta Neurol Scand* 1969;45:601–610.[PubMed]
71. Speight TM, Avery GS. Pizotifen (BC-105): a review of its pharmacological properties and its therapeutic efficacy in vascular headaches. *Drugs* 1972;3:159–203.[PubMed]
72. Freitag FG. Divalproex in the treatment of migraine. *Psychopharmacol Bull* 2003;37:98–115. Search date not reported.[PubMed]
73. El Amrani M, Massiou H, Bousser MG. A negative trial of sodium valproate in cluster headache: methodological issues. *Cephalalgia* 2002;22:205–208.[PubMed]
74. Monstad I, Krabbe A, Micieli G, et al. Preemptive oral treatment with sumatriptan during a cluster period. *Headache* 1995;35:607–613.[PubMed]
75. Wheeler SD, Carrazana EJ. Topiramate-treated cluster headache. *Neurology* 1999;53:234–236.[PubMed]
76. Forderreuther S, Mayer M, Straube A. Treatment of cluster headache with topiramate: effects and side-effects in five patients. *Cephalalgia* 2002;22:186–189.[PubMed]
77. Lainez MJ, Pascual J, Pascual AM, et al. Topiramate in the prophylactic treatment of cluster headache. *Headache* 2003;43:784–789.[PubMed]
78. Mathew NT, Kailasam J, Meadors L. Prophylaxis of migraine, transformed migraine, and cluster headache with topiramate. *Headache* 2002;42:796–803.[PubMed]
79. Leone M, Dodick D, Rigamonti A, et al. Topiramate in cluster headache prophylaxis: an open trial. *Cephalalgia* 2003;23:1001–1002.[PubMed]

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Disclaimer

TABLE 1 **The International Classification of Headache Disorders II (ICHD-II) diagnostic criteria for cluster headache.** [1]

Diagnostic criteria:

A. At least 5 attacks fulfilling 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
- forehead and facial sweating
- 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 1 every other day to 8 per day

E. Not attributed to another disorder

Episodic cluster headache

Description:

Occurs in periods lasting 7 days to 1 year separated by pain-free periods lasting 1 month or more

Diagnostic criteria:

All fulfilling criteria A–E above

At least 2 cluster periods lasting 7–365 days and separated by pain-free remissions of 1 month or more

Chronic cluster headache

Description:

Attacks occur for more than 1 year without remission or with remissions lasting less than 1 month

Diagnostic criteria:

All fulfilling criteria A–E above

Attacks recur over more than 1 year without remission periods or with remission periods of less than 1 month

GRADE **Evaluation of interventions for Cluster headache.**

Important outcomes					Headache relief				
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of interventions to abort cluster headache?									
2 (206) [29] [30]	Headache relief	Subcutaneous sumatriptan versus placebo	4	–3	0	0	0	Very low	Quality points deducted for no intention-to-treat analysis, incomplete reporting of results, and short follow-up
1 (118) [31]	Headache relief	Intranasal sumatriptan versus placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and for not reporting method of randomisation
2 (121) [32] [33]	Headache relief	Intranasal zolmitriptan versus placebo	4	–3	0	0	0	Very low	Quality points deducted for sparse data, unclear method of randomisation in one RCT, and incomplete reporting of results
1 (19) [34] [35]	Headache relief	High-dose and high-flow-rate oxygen versus placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and uncertainty about randomisation
1 (57) [38]	Headache relief	Subcutaneous octreotide versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (124) [39]	Headache relief	Oral zolmitriptan versus placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (13) [40] [34]	Headache relief	Hyperbaric oxygen therapy versus placebo	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and lack of randomisation. Directness point deducted for not including people with chronic cluster headache
What are the effects of interventions to prevent cluster headache?									
1 (23) [45]	Headache relief	Single greater occipital nerve injection versus placebo	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for inclusion of other interventions
1 (19) [46]	Headache relief	Corticosteroids versus placebo	4	–3	0	0	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and methodological flaws (no details on washout period and unclear whether reported data are pre- or post-crossover)
1 (30) [53]	Headache relief	Verapamil versus placebo	4	–3	0	0	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and for not reporting method of randomisation
1 (51) [58]	Headache relief	Ipsilateral versus contralateral capsaicin	4	–3	0	0	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and for weak methods (unclear level of blinding)
1 (28) [59]	Headache relief	Civamide (intranasal) versus placebo	4	–2	–1	0	0	Very low	Quality points deducted for sparse data and uncertainty about blinding. Consistency point deducted for different results at different end points
1 (96) [73]	Headache relief	Sodium valproate (oral) versus placebo	4	–3	0	0	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and methodological flaws (baseline difference between groups in duration of previous cluster bouts)
1 (169) [74]	Headache relief	Sumatriptan (oral) versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data

Important outcomes			Headache relief						
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.									