Acute and preventive pharmacologic treatment of cluster headache

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CRD summary
The authors recommend offering subcutaneous sumatriptan 6mg, intranasal zolmitriptan 5mg and 10mg and 100% oxygen for treatment of cluster headaches. Preventive therapies that should or may be considered were recommended in the review. Given the potential for missed data and the limited evidence for the different treatments, the authors’ recommendations should be interpreted with caution.

Authors’ objectives
To assess the effectiveness of treatments for the prevention of cluster headache attacks or reduction in headache severity.

Searching
MEDLINE (from 1950) and EMBASE (from 1980) were searched to June 2009. An updated search of MEDLINE was undertaken to February 2010. The full MEDLINE search strategy was reported in an on-line appendix.

Study selection
Prospective, double-blind, parallel-group or crossover randomised controlled trials (RCTs) that compared medication with placebo or another drug for treatment or prevention of chronic headache in adults aged 18 years and older with episodic or chronic cluster headache were eligible for inclusion. The primary outcomes were headache response (reduction from moderate, severe or very severe to mild or no pain) and pain-free response at 15 or 30 minutes, cessation of cluster headache attacks within a specific time period and number of days on which a cluster headache attack occurred. Adverse events were assessed.

Various drugs and regimens were used in the included studies: sumatriptan, zolmitriptan, 100% oxygen, cocaine, octreotide, dihydroergotamine, somatostatin, prednisone, cimamide, rapid- and long-acting steroids, sodium valproate, lithium, melatonin, misoprostol, verapamil, cimetidine, capsaicin and nitrate. Treatments were administered subcutaneously or through the nose in various forms (such as creams, nasal sprays and tablets).

Two reviewers independently screened studies for inclusion. Discrepancies were resolved through discussion.

Assessment of study quality
Study quality was assessed according to American Academy of Neurology criteria on allocation concealment, clear definition of primary outcomes, inclusion/exclusion criteria clearly defined, adequate accounting for dropouts and crossovers, and baseline comparability among treatment groups or appropriate adjustment for differences. RCTs were rated as Class I (all criteria met) to III (lacked two criteria).

The authors did not explicitly state how many reviewers performed the quality assessment.

Data extraction
Data were extracted as reported by the included studies, most frequently as response rate, time to response or number of events per week.

Two reviewers independently extracted data. Discrepancies were resolved through discussion.

Methods of synthesis
A fixed-effect model, or random-effects model where there was evidence of heterogeneity, was used to combine odds ratios (ORs) and 95% CIs by treatment type. Statistical heterogeneity was assessed using $X^2$ and $I^2$. Meta-analysis was only considered appropriate for some response rate data. Clinically heterogeneous studies were combined in a
narrative synthesis.

**Results of the review**

Twenty-seven RCTs (reported as 26 in the flow chart) (n=1,415 participants, range eight to 168) were included in the review. Twelve RCTs met all quality criteria (Class I), seven trials did not provide data on allocation concealment (Class II) and nine trials did provide data on allocation concealment and failed on at least one other criterion (Class III). Dropouts occurred in 17 RCTs (range zero to 33 patients).

**Acute treatment:**

Sumatriptan (three RCTs) 6mg and 12mg given subcutaneously was statistically significantly more effective than placebo for improved headache response at 15 minutes (OR 6.22, 95% CI 3.61 to 10.72; two RCTs). A third RCT showed that sumatriptan 20mg nasal spray was significantly more effective than placebo for headache response at 30 minutes (p=0.002).

Zolmitriptan (three RCTs) 5mg and 10mg was significantly more effective than placebo for improved headache response at 30 minutes when taken as a nasal spray (OR 5.03, 95% CI 2.81 to 9.01; two RCTs) or orally (one RCT).

Compared to regular air, 100% oxygen (two RCTs) was significantly more effective in relieving headache (p<0.01, one RCT) and resulting in pain-free response (p<0.001, one RCT).

One RCT each assessed cocaine/lidocaine, octreotide, dihydroergotamine, ergotamine, somatostatin and prednisone. Results were reported in the review.

**Preventive treatment:**

Lithium (two RCTs) 900mg showed significant improvement in the headache index compared to 360mg verapamil (p<0.01, one RCT). No significant differences were found in cessation of attacks between lithium 800mg and placebo (one RCT).

Verapamil (two RCTs) in one RCT showed that 360mg verapamil was significantly more effective than placebo in reducing headache attacks per day (p<0.001). The other RCT was listed above (under lithium).

Cimetidine/chlorpheniramine (two RCTs) showed no significant differences to placebo in the prevention of cluster attacks.

One RCT each assessed civamide, suboccipital steroid injection, sumatriptan, sodium valproate, melatonin, misoprostol, 100% hyperbaric oxygen, capsaicin, nitrate tolerance and prednisone. Results were reported in the review.

The most common adverse events were reported in the review.

**Authors’ conclusions**

For acute treatment of cluster headaches, sumatriptan 6mg given subcutaneously, intranasal zolmitriptan 5mg and 10mg and 100% oxygen should be offered as treatment (Level A advice). Intranasal sumatriptan 20mg and oral zolmitriptan 5mg and 10mg should be considered for treatment of cluster headaches (Level B advice).

For the prevention of cluster headaches, intranasal civamide 100μL and suboccipital steroid injection should be considered (Level B advice). Melatonin 10mg, verapamil 360mg and lithium 900mg may be considered (Level C advice).

**CRD commentary**

The review question was clear. Appropriate criteria were stated for study design, participants and outcomes, but were broad for interventions. The literature search was limited to two electronic databases. No attempts were made to locate
unpublished data, so potentially relevant data may have been missed. It was unclear whether language restrictions were applied. Study quality was assessed using appropriate criteria, but less than half of the trials were of highest quality. Study selection and data extraction were performed in duplicate, which reduced potential for reviewer error and bias; it was unclear whether the same was true for quality assessment.

The authors’ decision not to combine clinically heterogeneous trials was appropriate. Results for statistical heterogeneity were not reported. Only one or two trials provided evidence for the different treatments, which limited the robustness of the findings.

Two authors disclosed connections with pharmaceutical companies.

Given the potential for missed data and the heterogeneity among studies and limited evidence base for the different treatments, the authors’ conclusions should be interpreted with caution.

**Implications of the review for practice and research**

**Practice:** The authors stated that it was appropriate to initiate both acute symptomatic therapy and preventive therapy. Choice of treatments was based on headache frequency, patient comorbidities and side-effects.

**Research:** The authors stated that new treatments were emerging and in the future there may be a greater number of evidence-based treatment options for prevention of cluster headaches.

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