Pharmacological treatment of trigeminal neuralgia: systematic review and metanalysis

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CRD summary
This review assessed pharmacological treatments for trigeminal neuralgia. The authors concluded that carbamazepine is the drug of choice, and that lamotrigine and pimozide are indicated for cases refractory to conventional therapy. These conclusions are based on weak evidence and should be interpreted with caution.

Authors' objectives
To review randomised clinical trials on the efficacy, safety and tolerability of different trigeminal neuralgia drug treatments.

Searching
MEDLINE (1966 to July 2003), the Cochrane Controlled Trials Register (Issue 2, 2003), LILACS (1982 to July 2003), Biological Abstracts (1998 to July 2003) and Web of Science (1945 to July 2003) were searched. In addition, the references of relevant studies, meta-analyses and reviews were screened for further studies. Inclusion was restricted to publications in English, Spanish and Portuguese. Studies unavailable in Brazil were only included if study details were obtainable through the screening of relevant reviews.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion. Studies were excluded if it was unclear whether they were randomised or non-randomised.

Specific interventions included in the review
Trials investigating the use of drugs with analgesic effects were eligible for inclusion. The included studies used carbamazepine, tizanidine, tocainide, pimozide, proparacaine hydrochloride, lamotrigine, dextromethorphan and topiramate. The comparator was placebo or a different analgesic.

Participants included in the review
Trials enrolling participants diagnosed with typical active trigeminal neuralgia, according to usual criteria, were eligible for inclusion. Where reported, the proportion of women in the included study samples ranged from 43 to 93%, the mean age ranged from 53 to 65 years, and the disease duration ranged from 0.04 to 22 years up to 5 to 32 years.

Outcomes assessed in the review
The review set out to assess treatment efficacy, safety and tolerability. Treatment efficacy was based on the numbers of patients per treatment group presenting with lack of pain or mild pain (through the pain intensity scale), excellent, good or moderate response (through global treatment evaluation) or pain relief, or with more than a 50% decrease in pain score (through pain intensity or neuropathic scale). Treatment safety referred to the number of patients with adverse effects. Tolerability referred to the number of patients dropping out of the study due to adverse events.

How were decisions on the relevance of primary studies made?
Three independent reviewers assessed the search results for articles eligible for inclusion in the review. Any disagreements were settled by consensus.

Assessment of study quality
Allocation concealment in the studies was classified using the criteria in the Cochrane Reviewers' Handbook. The Jadad scale was used to assess study quality. Two independent reviewers assessed the validity of the studies. Any disagreements were settled by consensus.
Data extraction
Two or more independent reviewers extracted the data.

Methods of synthesis
How were the studies combined?
The individual study results were presented in a narrative synthesis. The odds ratios (ORs) and 95% confidence intervals (CIs) of some studies were pooled in a meta-analysis; a fixed-effect model was applied.

How were differences between studies investigated?
Heterogeneity was assessed statistically using the chi-squared test.

Results of the review
Thirteen studies (n=352) met the inclusion criteria. The included studies employed parallel (2 studies) and crossover (11 studies) designs.

In terms of quality, the studies scored from 3 to 5 points out of a possible 5 (mean score 4 out of 5).

Carbamazepine versus placebo: carbamazepine was superior to placebo in all 6 identified studies (pooled OR 0.01, 95% CI: 0.01, 0.04; based on 4 studies, n=100).

Other drugs versus placebo: in 3 trials comparing lamotrigine, topiramate or 0.5% proparacaine hydrochloride, respectively, with placebo, only lamotrigine was superior to placebo (1 study, n=14).

Carbamazepine versus other drugs: in 3 trials comparing carbamazepine with, respectively, tizanidine, tocainide or pimozide, only pimozide had a greater favourable effect than carbamazepine (n=48, P<0.001).

Other comparisons: one study comparing dextromethorphan with low-dose lorazepam showed increased pain in the former group (n=2 and 1 drop-out).

In terms of safety, 2 studies of carbamazepine reported side-effects for half of the patients (in 1 study 24% of the placebo group showed side-effects as well), another showed incidences of sleepiness, vertigo and stomach discomfort, and a further study reported severe toxic effects of the drug for several patients. In 3 studies up to 3 patients dropped out because of adverse events. Various adverse events were also reported in trials of lamotrigine, topiramate, dextromethorphan, tocainide and pimozide, with one drop-out reported for side-effects of tocainide.

Authors' conclusions
Carbamazepine is the drug of choice for treating trigeminal neuralgia; for cases refractory to conventional therapy, lamotrigine and pimozide are indicated.

CRD commentary
This review had a clear question and inclusion criteria, and the review process was well reported. The search encompassed several electronic databases, and attempts were made to locate unpublished studies by screening the reference lists of relevant studies. The review was restricted to studies published in English, Spanish and Portuguese, and obtainable in Brazil, which leaves some scope for publication and language bias. Measures to reduce errors and bias in the study selection procedure (i.e. the use of several independent reviewers) were taken. The validity of the included studies was assessed using adequate criteria.

The statistical synthesis of the review was difficult to follow: the continuous treatment effect outcomes were translated into statistically less informative dichotomous outcomes; the odds ratio rather than the risk ratio was calculated as the effect size measure; only a selection of studies was used for the pooled analysis; and it was unclear how the characteristics of the crossover trial were taken into account in the meta-analysis (potentially doubling the number of
patients in the RevMan analysis). Several included studies were based on very small samples, which weakens the reliability and validity of the primary studies the synthesis was based on. In addition, apart from the comparison of carbamazepine with placebo, there was only one study of each drug comparison. The review’s conclusions are therefore based on weak evidence and should be interpreted with caution.

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

**Practice:** The authors stated that patients undergoing prolonged treatment with carbamazepine, especially the elderly, should be monitored for blood and skin reactions and subjected to liver and renal function tests and blood cell counts.

**Research:** The authors stated that high-quality clinical trials on the efficacy, safety and tolerability of different drugs for the treatment of trigeminal neuralgia are needed. Outcomes should be simplified to binary data. More research is needed to identify the best treatment for different patient groups.

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