Migraine prophylactic drugs: proof of efficacy, utilization and cost

Ramadan N M, Schultz L L, Gilkey S J

Authors' objectives
To review the scientific rigour of published trials of the efficacy of migraine prophylactic drugs, assess their cost and test the correlation between utilisation, scientific rigour and cost.

Searching
Reports published in the English language were sought from the following sources: MEDLINE, reference lists of publications extracted from this search, review of Headache books and proceedings of the American Academy of Neurology, the International Headache Congress, the Migraine Trust and the American Association for the Study of Headache.

Study selection
Study designs of evaluations included in the review
Randomised, double-blind placebo controlled trials of migraine prophylaxis drugs were included. Studies which did not include a placebo arm during the active phase were excluded and studies in which more than one drug was studied were included, only if there was a placebo treatment during the active phase of the study.

Specific interventions included in the review
The interventions studied included the following drugs used for migraine prophylaxis: beta-blockers including acebutolol, pindolol, oxprenolol, alprenolol, timolol, nadolol and metoprolol; calcium-channel blockers including nifedipine, flunarizine, verapamil and nimodipine; non-steroidal anti-inflammatory drugs including naproxen, aspirin, indobufen, fenoprofen, ketoprofen, flurbiprofen and tolfenamic acid; serotonin-active drugs including pizotifen and dihydroergotamine, tricyclics including amitryptiline; anticonvulsants including divalproex and carbamazepine, methysergide, fluoxetine and clonidine.

Participants included in the review
Patients treated with migraine prophylactic drugs were included. No other details were provided.

Outcomes assessed in the review
The main outcome from the primary studies was the efficacy of the active drug over placebo, assessed by headache frequency. The following outcomes were also assessed: scientific rigour of studies and utilisation data obtained from 100 neurologists and 96 primary care physicians in the USA about their preference for first and second choice migraine prophylactic therapy.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
All included trials were rated on a five-point scale (1 = low to 5 = good, with negative scores given for trials in which the drug was not superior to the placebo), by a reviewer blinded to data on utilisation and cost of the drugs. The following criteria were used to assess the validity of primary studies: recommendations of the International Headache Society Committee on Clinical Trials in Migraine, the level of description of the methodology, drop-out rate, sample size, appropriateness of the chosen statistical methods and the presentation of the results. The authors do not state how the papers were assessed for validity, or how many of the authors performed the validity assessment.

Data extraction
The following data were extracted: article source, first author, study drug and dose, sample size, criteria use to diagnose migraine, drop-out rate and reasons, type of study, outcome measures and results. The average scientific score (ss) was computed for each drug separately.

Methods of synthesis
How were the studies combined?
The average scientific score (ss) was computed separately for each drug. Negative scores given to studies indicate that the results did not favour the active drug over the placebo. The studies were combined in a narrative review.

How were differences between studies investigated?
Some differences were discussed in the light of scores for scientific rigour.

Results of the review
There were 33 randomised controlled trials (RCTs) of beta-blockers, 3 RCTs of tricyclics, 18 RCTs of calcium-channel blockers, 5 RCTs of anti-convulsants, 14 RCTs of non-steroidal anti-inflammatory drugs, 12 RCTs of serotonin-active drugs, 2 RCTs of SSRIs, 3 RCTs of anti-serotonin agents, and 6 RCTs of clonidine.

Beta-blockers: the ss of drugs studied and the number of trials involved are as follows:
Propranolol (18 RCTs) ss = 1.44; Atenolol (3 RCTs) ss = 2.33; Timolol (3 RCTs) ss = 3.00; Nadolol (1 RCT) ss = 1.00; Acebutolol (1 RCT) ss = -1.00; Pindolol (2 RCT) ss = -1.00; Oxprenolol (1 RCT) ss = -1.00; Alprenolol (1 RCT) ss = -1.00, Metoprolol (3 RCTs) ss = 4.33. Tricyclics: Amitryptyline (3 RCTs) ss = 2.33.
Calcium channel blockers: Verapamil (4 RCTs) ss = 1.00; Nimodipine (6 RCTs) ss = -0.83; Nifedipine (2 RCTs) ss = -0.5; Flunarizine (6 RCTs) ss = 2.17.
Non-Steroidal Anti-Inflammatory Agents: Naproxen (6 RCTs) ss = 2.17; Aspirin (2 RCTs) ss = -0.67; Indobufen (1 RCT) ss = 5.00; Fenoprofen (1 RCT) ss = 3.00; Ketoprofen (1 RCT) ss = 1.00; Flurbiprofen (1 RCT) ss = 5; Tolfenamic Acid (2 RCTs) ss = 5.00.
Anti-convulsants: Divalproex (4 RCTs) ss = 3.75; Carbamazepine (1 RCT) ss = 1.00.
SSRIs: Fluoxetine (2 RCTs) ss = 0.00.
Anti-serotonin agents: Methylsergide (3 RCTs) ss = 1.33.
Serotonin Active Drugs: Pizotifen (10 RCTs) ss = 1.10; Dihydroergotamine (2 RCTs) ss = 2.50.
Others: Clonidine (6 RCTs) ss = 0.00.

38% of neurologists reported using Beta-blockers as the first line with 21% using this class of agents as a second line. Primary care physicians were in line with neurologists. Propranolol was the most popular beta-blocker. Tricyclic antidepressants and calcium channel blockers ranked second and third.

Overall, Spearman's rank correlation between neurologists' choice of first or second line of therapy and scientific proof of efficacy was strong (c) = 0.644, P = 0.018). Good correlation was found between primary care physicians' choice and scientific proof of efficacy (c) = 0.576, P = 0.050).

No correlation was found between physicians preference and cost of drugs (neurologist: r = -0.254, P = 0.450; primary care physician: r = -0.255, P = 0.455).

Cost information
The average wholesale price for each drug was obtained from data published by Adelman and Von Seggern and from...
the Amerisource catalogue (7/6/96). The average of each daily dose reported in the different trials of a specific drug was used to calculate the average monthly cost of that medication.

**Authors’ conclusions**
The three most commonly chosen migraine prophylactic agents have not been shown to irrefutably prevent migraine. Their benefit, if any, does not exceed 50% over placebo. Physicians’ choice of agent remains largely empiric. Until a drug which is demonstrated to be the "ideal migraine preventative agent" is found, it is difficult to argue that one migraine prophylactic medication is superior to another.

**CRD commentary**
The primary studies were assessed and scored for validity according to pre-defined criteria and the discussion includes comment on some of the limitations of the review, including the lack of evaluation of inter- and intra-rater variability, lack of comparison of the incidence and severity of adverse reactions, limiting the literature search to published articles in the English language and the problems arising from the variable methodology, outcome measures and generally poor quality of the primary studies. Reasons are given for not performing a meta-analysis.

Details are lacking of the methods used to select studies for inclusion and to extract data. Fuller details of the individual trials would have been welcome such as the number of subjects, patient characteristics, inclusion criteria for subjects, ascertainment of outcomes, outcome measures used, active period, follow-up period and method of randomisation. The individual scoring of the trials for validity does not appear to have been blinded to the results of the studies. Although mention is made of heterogeneity among trials, this heterogeneity is neither assessed statistically nor discussed in any detail. The score for scientific rigour is presented as an unweighted average which incorporates the outcome. It may have been more appropriate to report the validity scores separately and undertake some sensitivity analysis to investigate any heterogeneity.

Without fuller relevant details of the primary studies it is not possible to assess the quality of the selected studies and hence evaluate the evidence offered.

**Implications of the review for practice and research**
Good quality trials which are reported in detail are required to determine the most cost-effective therapy for migraine prevention.

**Bibliographic details**

**PubMedID**
9137841

**Other publications of related interest**

**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Adult; Amitriptyline /economics /pharmacology /therapeutic use; Female; Humans; Male; Migraine Disorders /drug therapy /prevention & control; Propranolol /economics /pharmacology /therapeutic use; Verapamil /economics /pharmacology /therapeutic use
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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.