Efficacy and tolerability of frovatriptan in acute migraine treatment: systematic review of randomized controlled trials

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CRD summary
This review assessed the efficacy and tolerability of frovatriptan for the treatment of acute migraine. The authors concluded that frovatriptan is more effective than placebo for the acute treatment of moderate to severe migraine, but it increases adverse effects. There were limitations in the reporting of the review methods but, overall, the authors' conclusions appear reliable.

Authors' objectives
To evaluate the efficacy and tolerability of frovatriptan for the treatment of acute migraine.

Searching
MEDLINE, EMBASE, EMB Reviews and the Cochrane Library were searched from inception to February 2005 using the reported search terms. No language restrictions were applied. The reference lists of RCTs and reviews were screened.

Study selection
Study designs of evaluations included in the review
Double-blind randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies that compared frovatriptan 2.5 mg with placebo were eligible for inclusion.

Participants included in the review
Studies of patients with acute moderate to severe migraine were eligible for inclusion. Studies of patients with mild migraine were not included.

Outcomes assessed in the review
Studies that assessed the percentage of patients who became pain-free or the percentage with headache response, headache recurrence, or relief of migraine-related symptoms (nausea, photophobia and phonophobia) were eligible for inclusion. Headache response was defined as the percentage of patients whose headache severity changed from moderate or severe (grade 2,3) to mild or none (grade 0,1) according to International Headache Society (IHS) criteria. In the review, the headache recurrence rate was defined as the proportion of patients whose headache was relieved at 4 hours but recurred within 24 hours of the initial drug dose. Efficacy outcomes (percentage pain-free, headache severity and symptoms associated with migraine) were assessed at 2 and 4 hours. The review also assessed adverse effects.

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

Assessment of study quality
Where adequate information was presented, the validity of the included studies was assessed and scored using the Jadad scale. This scale considers randomisation, blinding and the handling of withdrawals. The maximum possible score was 5 points. The authors did not state how the validity assessment was performed.

Data extraction
Two reviewers independently extracted the data on an intention-to-treat basis and resolved disagreements through consensus. One report of three studies was treated as three separate studies. For each study, the number of patients with each outcome of interest was extracted for each treatment arm and the risk ratio (RR) and risk difference (RD), together with their respective 95% confidence intervals (CIs), were calculated.

**Methods of synthesis**

How were the studies combined?

Pooled RRs and RDs and their 95% CIs were calculated; the studies were weighted by inverse variance. A random-effects model was used where statistically significant heterogeneity ($p<0.1$) was identified. The numbers-needed-to-treat (NNT) or to-harm were calculated, together with their respective 95% CIs, from the pooled estimates of RD.

How were differences between studies investigated?

Heterogeneity was assessed using the Q statistic.

**Results of the review**

Five RCTs ($n=2,866$) were included. Three of these RCTs were summarised in one report.

The two RCTs presenting adequate information scored 3 out of 5 on the Jadad scale.

No statistically significant heterogeneity was found for any of the meta-analyses of efficacy outcomes.

The pooled analysis showed a statistically significant increase in the proportion of pain-free patients with frovatriptan compared with placebo: the RR was 3.70 (95% CI: 2.59, 5.29, $p<0.0001$) at 2 hours and 2.67 (95% CI: 2.21, 3.22, $p<0.0001$) at 4 hours; the NNT were 12 (95% CI: 10, 15) and 6 (95% CI: 5, 7), respectively.

The pooled analysis showed a statistically significant increase in the proportion of patients with headache response with frovatriptan compared with placebo: the RR was 1.66 (95% CI: 1.47, 1.88, $p<0.0001$) at 2 hours and 1.83 (95% CI: 1.66, 2.00, $p<0.0001$) at 4 hours; the NNT were 7 (95% CI: 6, 9) and 4 (95% CI: 4, 5), respectively.

The pooled analysis showed a statistically significant decrease in the proportion of patients with headache recurrence with frovatriptan compared with placebo: the RR was 0.74 (95% CI: 0.59, 0.93, $p=0.0093$); the NNT was 17 (95% CI: 9, 100).

The pooled analysis showed that frovatriptan statistically significantly reduced the risk of nausea (RR 0.86, 95% CI: 0.80, 0.94, $p=0.0005$ and NNT 15 at 2 hours; RR 0.63, 95% CI: 0.57, 0.70, $p<0.0001$ at 4 hours), photophobia (RD 17%, 95% CI: 12, 22, $p<0.0001$ at 2 hours; RD 34%, 95% CI: 29, 39, $p<0.0001$ at 4 hours) and phonophobia (RD 14%, 95% CI: 7, 20, $p<0.0001$ at 2 hours; RD 30%, 95% CI: 23, 36, $p<0.0001$ at 4 hours).

The pooled analysis showed that frovatriptan significantly increased the risk of adverse effects compared with placebo: RR 1.31 (95% CI: 1.07, 1.62, $p=0.0106$) and NNH 10 (95% CI: 6, 50), based on two RCTs. The most common adverse effects with frovatriptan were dizziness, nausea, fatigue and paresthesia.

**Cost information**

No (see Other Publications of Related Interest no.1).

**Authors' conclusions**

The findings suggest that frovatriptan is more effective than placebo for the acute treatment of moderate to severe migraine, but it increases adverse effects. The effectiveness of frovatriptan, relative to more established agents, needs to be ascertained.

**CRD commentary**
The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. Four relevant databases were searched without language restrictions, which reduces the potential for language bias. No attempts were made to locate unpublished studies, thus raising the possibility of missing relevant data and publication bias. Methods were used to minimise reviewer errors and bias in the extraction of data, but it was unclear whether similar steps were taken at the study selection and validity assessment stage. Only double-blind RCTs were included. Two of the five included RCTs reported sufficient information to allow an assessment of validity but only composite validity scores were presented, making it difficult for readers to judge study validity for themselves. Since the validity of the other three RCTs was not assessed, it is not possible to comment adequately on the reliability of the results presented for these studies. Statistical heterogeneity was assessed and studies were appropriately combined in meta-analyses. There were limitations in the reporting of the review methods but, overall, the authors’ conclusions appear reliable.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that there is a need for head-to-head comparisons of frovatriptan with other active drugs to determine the role of frovatriptan in the acute treatment of migraine headaches.

Bibliographic details

PubMedID
16336284

DOI
10.1111/j.1365-2710.2005.00677.x

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Carbazoles /adverse effects /therapeutic use; Double-Blind Method; Humans; Meta-Analysis as Topic; Migraine Disorders /drug therapy; Randomized Controlled Trials as Topic; Treatment Outcome; Tryptamines /adverse effects /therapeutic use

AccessionNumber
12006003253

Date bibliographic record published
30/04/2007

Date abstract record published
30/04/2007
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.