Systematic review: direct comparative trials of the efficacy of proton pump inhibitors in the management of gastro-oesophageal reflux disease and peptic ulcer disease

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CRD summary
This review assessed the efficacy of proton-pump inhibitors in treating gastro-oesophageal reflux and peptic ulcer disease, and concluded that insufficient evidence was available to establish the superiority of any one agent. A limited search and language restrictions mean that studies might have been missed. The broad conclusion seems appropriate, however, the specific conclusions and implications for practice should be treated with caution.

Authors' objectives
To identify differences in efficacy between proton-pump inhibitors (PPIs) in the treatment of gastro-oesophageal reflux disease (GERD) and peptic ulcer disease (PUD).

Searching
MEDLINE was searched from 1988 to 2002 for studies published in full and in English; the search terms were reported. The reference lists of potentially relevant studies were also checked.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies of PPIs compared with each other or different doses of a specific PPI were eligible for inclusion. The included studies used lansoprazole (15 to 30 mg), omeprazole (10 to 40 mg), pantoprazole (40 mg), rabeprazole (10 to 20 mg) and esomeprazole (20 to 40 mg).

Participants included in the review
Studies of patients with GERD or PUD were eligible for inclusion. Studies of functional dyspepsia were included if the results for those with GERD or PUD were reported in full. The included studies were conducted in patients with GERD with and without oesophagitis, oesophagitis plus stricture, and duodenal and gastric ulcers.

Outcomes assessed in the review
Studies reporting a measurable relevant end point, such as healing of the oesophagus, duodenal or gastric ulcer, or symptom relief, were eligible for inclusion. The review assessed healing and symptom relief in GERD, maintenance of healing of GERD, and healing and maintenance of healing of ulcers.

How were decisions on the relevance of primary studies made?
Two reviewers assessed studies for relevance, with any differences resolved by consensus.

Assessment of study quality
Study quality was assessed using the Jadad scale, which evaluates randomisation, allocation concealment, and the reporting of drop-outs and withdrawals, to give a score of 0 to 5. Only RCTs with a score of 3 or above were included in the review. Two reviewers assessed study quality, with any differences resolved by consensus.

Data extraction
Two reviewers extracted the data using standardised forms, with any differences resolved by consensus. The
percentages of patients reporting the outcomes of interest were extracted.

**Methods of synthesis**
How were the studies combined?
The study results were combined in a narrative.

How were differences between studies investigated?
Some study details were presented in tabular format, ordered by intervention and then outcome measure.

**Results of the review**
Thirty-two studies were included in the review. The number of patients in each study was not reported.

Lansoprazole versus other PPIs.

Studies found that 30 mg lansoprazole was superior to 20 mg omeprazole for the healing of oesophagitis (1 study) and symptom relief of GERD (1 study). Similar efficacy was reported for 30 mg lansoprazole, 20 or 40 mg omeprazole (2 studies), or 40 mg pantoprazole (1 study) in the healing of oesophagitis. Lansoprazole 30 mg was inferior to 20 mg omeprazole for the prevention of relapse of oesophagitis and stricture (1 study), but was similar to omeprazole for the maintenance of healing of oesophagitis (2 studies). Lansoprazole 30 mg demonstrated similar efficacy to 20 mg omeprazole for the healing and maintenance of healing of ulcers (2 studies). Lansoprazole 15 mg was less effective than a dose of 30 mg in the healing of erosive oesophagitis (1 study), but had similar efficacy in the healing and maintenance of healing of ulcers (1 study).

Pantoprazole versus other PPIs.

The healing rates were similar for standard doses of 40 mg pantoprazole and 20 mg omeprazole (3 studies).

Rabeprazole versus other PPIs.

The efficacy of 20 mg rabeprazole was similar to that of 20 mg omeprazole for all outcomes (3 studies). A dose of 10 mg rabeprazole had similar efficacy to one of 20 mg in the maintenance of healing of GERD (1 study).

Esomeprazole versus other PPIs.

Studies found that 40 mg esomeprazole was superior to 20 mg omeprazole (2 studies) and 30 mg lansoprazole (1 study) in the healing of oesophagitis and time to sustained heartburn relief (3 studies). A dose of 20 mg esomeprazole had similar efficacy to one of 40 mg in the relief of symptoms of GERD (2 studies).

Omeprazole.

Studies found that 10 mg omeprazole was less effective than 20 mg in the treatment of GERD symptoms (1 study), but had similar efficacy in symptom relief in people without oesophagitis (1 study). A dose of 20 mg omeprazole had similar efficacy to one of 40 mg in symptom relief in people without oesophagitis (1 study), whereas 40 mg omeprazole was more effective than 20 mg for the healing of gastric ulcers (1 study).

**Authors' conclusions**
There was insufficient evidence to establish the superiority of any one agent over all others across all disease states.

**CRD commentary**
The review question was clear in terms of the intervention, participants, outcomes and study design. Only one electronic database was searched, and only full publications in English were included, therefore the potential for publication and language bias is high. Each stage of the review was conducted in duplicate, thus reducing the potential
for error and bias. The decision to combine the studies using a narrative synthesis was appropriate given the clinical heterogeneity of the included studies. Differences between the studies were not discussed, and inadequate study details were provided to assess differences; in particular, the number of participants in each study was not reported, drop-outs were not considered, and it was not possible to assess the comparability of definitions of outcomes across studies. The limited search and language restriction mean that the results may not reflect the entirety of the literature on this subject. Only one or two studies were identified for each combination of treatment and disease condition. Given these limitations, the broad conclusion that there was insufficient evidence to establish the superiority of any one agent over all others across all disease states seems appropriate. However, the more specific conclusions and implications for practice should be treated with caution.

Implications of the review for practice and research
Practice: The authors stated that the use of low-dose PPIs for the healing and symptom relief of GERD cannot be recommended. However, low doses can be recommended for the maintenance of the healing of oesophagitis and peptic ulcers.

Research: The authors suggested that adequately powered studies are required to determine the effectiveness of low doses and whether any PPI is superior to others for different classes of disease, using meaningful clinical outcomes. Head-to-head studies investigating healing, symptom relief and safety, and evaluations of newer agents, are also recommended.

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