Effects of proton-pump inhibitors on functional dyspepsia: a meta-analysis of randomized placebo-controlled trials


CRD summary
The authors concluded that for patients with ulcer-like and reflux-like dyspepsia, proton-pump inhibitors are more effective than placebo. This was a well-conducted review and the authors' conclusions are likely to be reliable.

Authors' objectives
To evaluate the efficacy of proton-pump inhibitors (PPIs) for the treatment of patients with functional dyspepsia.

Searching
PubMed, MEDLINE, EMBASE, CINAHL and the Cochrane Controlled Trials Register were searched through September 2005 without any language restrictions; the search terms were reported. In addition, abstracts from meetings of four specified major gastrointestinal meetings from the previous 8 years and references of identified studies were screened.

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

Specific interventions included in the review
Studies that compared PPIs with placebo were eligible for inclusion. Studies that evaluated combinations of treatments were excluded. The included studies evaluated lansoprazole (15 or 30 mg) for between 2 and 8 weeks and omeprazole (10 or 20 mg) for 2 or 4 weeks.

Participants included in the review
Studies of adults with functional dyspepsia (defined as persistent or recurrent dyspepsia with no evidence of organic disease) were eligible for inclusion. Studies of patients with the following diagnoses were excluded: gastroesophageal reflux disease, peptic ulcer disease, non-steroidal anti-inflammatory drug-related gastropathy, irritable bowel syndrome, and biliary tract or pancreatic disease. The included studies were in patients with ulcer-like dyspepsia, reflux-like dyspepsia, dysmotility-like dyspepsia and unspecifed dyspepsia. In the included studies, the mean age of the participants was 43.1 years and 37% were male.

Outcomes assessed in the review
Studies were required to report data on treatment success. This could be defined as no symptoms, no symptoms for further management, or an improvement in gastrointestinal rating scale post-treatment. Most of the included studies defined complete relief as no symptoms within a given number of final days of treatment; other studies used different definitions, including scores on the gastrointestinal symptom rating system.

How were decisions on the relevance of primary studies made?
Three reviewers independently conducted the searches. No further details were reported.

Assessment of study quality
Two reviewers independently assessed validity and resolved any differences by reaching consensus. The studies were assessed for study design, blinding, method of randomisation, criteria used to diagnose dyspepsia, baseline characteristics, patient compliance, outcome measures and intention-to-treat (ITT) analysis, and were ranked using these criteria.
Data extraction
Two reviewers independently extracted the data and resolved any differences by reaching consensus. For each study, the number of patients with improvement and the number showing Helicobacter pylori (H. pylori) infection before and after treatment were extracted on an ITT basis. The relative risk (RR) and relative risk reduction (RRR) of treatment success were calculated, along with the 95% confidence intervals (CIs).

Methods of synthesis
How were the studies combined?
The pooled RR and RRR were calculated, along with 95% CIs, using a random-effects model. The number-needed-to-treat (NNT), with 95% CI, was also calculated. The potential for publication bias was assessed using the funnel plot suggested by Egger et al.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the Q statistic. The influence of each study was assessed by repeating the analysis after omitting each study in turn. Studies responsible for significant heterogeneity were identified and potential causes discussed. Meta-regression was used to examine the influence on the results of PPI dose and duration of treatment, the proportion of patients with the predominant symptoms, the proportion of patients with H. pylori infection and some aspects of study quality. A sensitivity analysis was used to examine the influence of format of publication (abstract or full publication). Subgroups of patients with different types of dyspepsia were also analysed separately.

Results of the review
Seven RCTs (n=3,725) were included.

PPIs were associated with a statistically significant improvement in treatment success compared with placebo, 40.3% versus 32.7%; the RRR was 10.3% (95% CI: 2.7, 17.3) and the NNT was 14.6 (95% CI: 8.7, 57.1). The exclusion of one study published only as an abstract did not significantly change this result. Statistically significant heterogeneity was present (p=0.0005). The meta-regression found no significant relationship between treatment success and the proportion of patients with the predominant reflux-like symptoms, the proportion of patients with H. pylori infection, the PPI dose and duration of PPI treatment, and study quality criteria to explain the heterogeneity. However, the omission of one RCT that included Chinese patients resulted in statistical homogeneity (p=0.20) without any major change in the results (RRR 14.7%, 95% CI: 9.5, 19.5).

Low-dose and standard-dose PPI, when examined separately, were both associated with improvements in treatment success compared with placebo, but the improvements were not statistically significant.

For H. pylori-positive patients (6 studies, n=1,394), PPIs were associated with a statistically significant reduction in symptoms compared with placebo (RRR 13.3%, 95% CI: 5.1, 20.9). No significant heterogeneity was found. For H. pylori-negative patients (7 studies, n=2,284), there was no statistically significant difference in symptom relief between PPIs and placebo (RRR 5.7%, 95% CI: -5.3, 15.5).

PPIs were associated with a statistically significant improvement in treatment success compared with placebo in patients with ulcer-like dyspepsia (3 studies; RRR 12.8%, 95% CI: 7.2, 18.1) and patients with reflux-like dyspepsia (3 studies; RRR 19.7%, 95% CI: 1.8, 34.3). No significant heterogeneity was found for either analysis (p=0.88 and p=0.10, respectively). There were was no significant differences in symptom relief between PPIs and placebo in patients with dysmotility-like dyspepsia (3 studies) and unspecified dyspepsia (4 studies).

The funnel plot was symmetrical, suggesting no evidence of publication bias.

Authors' conclusions
For patients with ulcer-like and reflux-like dyspepsia, PPIs are more effective than placebo.
CRD commentary
The review addressed a clear question that was defined in terms of the intervention, participants, outcomes and study design. Several relevant sources were searched and attempts were made to minimise language bias; the potential for publication bias was assessed and no evidence of it was found. The validity of the included studies was assessed using specified criteria and the results were reported. Adequate information about the included studies was provided. At least two reviewers independently selected studies, assessed validity and extracted the data, thus reducing the potential for reviewer bias and errors. The studies were combined in a meta-analysis, statistical heterogeneity was assessed, and potential sources of heterogeneity were examined. This was a well-conducted review and the authors' conclusions are likely to be reliable.

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

Research: The authors stated the need for further RCTs to evaluate the effects of PPIs in patients with H. pylori-positive and H. pylori-negative functional dyspepsia. Studies evaluating the effects of different PPI regimens, including stopping PPIs, intermittent PPIs and on-demand PPI use, are also required.

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