Systematic review: is there excessive use of proton pump inhibitors in gastro-oesophageal reflux disease?

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CRD summary
This review assessed alternatives to continuous proton-pump inhibitor (PPI) treatment for gastrooesophageal reflux disease. The authors concluded that evidence supported on-demand PPI treatment of endoscopy-negative reflux disease, but there was less support for on-demand treatment of erosive oesophagitis. Incomplete reporting of review methods and limited information on study outcomes and results make the reliability of the conclusions uncertain.

Authors' objectives
To assess the effects of alternatives to continuous proton-pump inhibitors (PPIs) for the long-term treatment of gastrooesophageal reflux disease (GERD).

Searching
MEDLINE and EMBASE were searched from inception onwards using the reported search terms. Reference lists from identified articles and reviews were screened. The authors of primary studies reported as abstracts were contacted for additional information. Pharmaceutical companies were contacted for additional or unpublished data. English and non-English language reports were eligible.

Study selection
Study designs of evaluations included in the review
Observational and intervention studies were eligible for inclusion. Intervention studies had to report information about the selection of patients and the treatments used. Reviews were excluded. The included interventional studies were non-randomised observational studies and RCTs.

Specific interventions included in the review
Studies of PPI treatments compared with alternative PPI treatments or placebo were eligible for inclusion. The review assessed the effects of intermittent PPI treatment, on-demand PPI treatment, and ‘step-down’ and ‘step-up’ treatment. The studies used omeprazole, esomeprazole, lansoprazole and ranitidine (full details of treatment regimens were reported). Four studies compared intervention groups with placebo and twelve with alternative PPI treatments.

Participants included in the review
Studies in patients with GERD were eligible for inclusion. The included studies were in patients with erosive oesophagitis (EE), endoscopy-negative reflux disease (ENRD) and uninvestigated heartburn. One study that included a majority of patients who did not have GERD was also included. Most of the randomised controlled trials (RCTs) were conducted in patients who had responded to prior continuous PPI treatment. The age range of the patients was between 14 and 91 years.

Outcomes assessed in the review
Studies that only reported an economic analysis were excluded; no other inclusion criteria for the outcomes were defined. The included studies assessed a variety of outcomes: successful completion of treatment, percentage of patients willing to continue their allocated regimen, percentage of patients who discontinued their allocated regimen, percentage with insufficient control of symptoms, level of symptom control, patient satisfaction with treatment, percentage of heartburn-free periods and consumption of antacids.

How were decisions on the relevance of primary studies made?
Two reviewers conducted the searches and three selected the studies. Any disagreements were resolved through consensus.
Assessment of study quality
The validity of the RCTs was assessed and scored using the Jadad scale, which considers the reporting and methods of randomisation, blinding and withdrawals. The maximum possible score was 5 points. The authors did not state that they assessed the validity of non-randomised studies.

The authors did not state who performed the validity assessment.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. A summary of the principal outcomes was extracted for each study.

Methods of synthesis
How were the studies combined?
The studies were grouped by study design (RCT and other) and combined in a narrative.

How were differences between studies investigated?
The results for RCTs were further grouped by treatment regimen. Some differences between the studies were evident from the data tables, while others were discussed in the text.

Results of the review
Sixteen studies were included (n at least 13,374): 9 RCTs (n=5,771) and 7 observational studies (n at least 7,603).

RCTs.
In terms of study quality, the Jadad scores ranged from 1 to 5 points. Four RCTs scored 4 or more points. Five of the 9 RCTs failed to report an adequate method of randomisation and were only awarded one out of a possible 2 points for this criterion.

Intermittent PPI treatment. One RCT (704 patients with EE or ENRD) reported that one year of intermittent treatment (2- to 4-week courses) was successfully completed in 48% allocated to omeprazole 20 mg, 46% allocated to omeprazole 10 mg and 47% allocated to ranitidine. Patients experienced between 273 and 279 days in 12 months off treatment with PPI or H2-receptor antagonist.

On-demand PPI treatment.
One RCT (421 patients with GERD but without EE) reported that the percentage of patients willing to continue their allocated regimen at 6 months was 83% for omeprazole 20 mg, 69% for omeprazole 10 mg (P<0.01 for 10 mg versus 20 mg) and 56% for placebo (P<0.001 versus 20 mg omeprazole and P<0.01 versus omeprazole 10 mg). Patients taking placebo consumed more antacid tablets.

One RCT (342 patients with GERD but without EE) reported a statistically significantly higher percentage of patients who had discontinued treatment by 6 months because of insufficient control of heartburn with placebo compared with esomeprazole 20 mg (52% versus 14%, P<0.0001). Patients taking placebo consumed significantly more antacid tablets.

One RCT (721 patients with ENRD) reported that the percentage of patients who discontinued their allocated regimen at 6 months was 11% for esomeprazole 40 mg, 8% for esomeprazo 20 mg and 42% for placebo. Significantly more patients taking esomeprazole were free from gastrointestinal symptoms at 6 months compared with placebo.

One RCT (100 patients with grade A or B endoscopically diagnosed EE entered; 66 patients whose symptoms resolved with initial treatment took on-demand treatment) reported similar levels of symptom control at 4 to 8 weeks between patients taking on-demand esomeprazole 40 mg or omeprazole 20 mg and those taking continual daily dosing. On-demand treatment with omeprazole 20 mg was superior to continuous treatment in controlling GERD symptoms.
One RCT (1,052 patients with GERD with EE or ENRD) reported that the percentage of patients 'quite satisfied' or 'completely satisfied' with their treatment by 6 months was 89.6% for continuous omeprazole 20 mg and 88.4% for esomeprazole 40 mg.

One RCT (418 patients with GERD) reported that the number of patients discontinuing their allocated regimen by 6 months was 16 out of 279 for rabeprazole 10 mg and 28 out of 137 for placebo (P<0.00001).

One RCT (1,471 patients with GERD) reported similar levels of patient satisfaction for on-demand esomeprazole 20 mg and intermittent esomeprazole 40 mg daily for 2 to 4 weeks.

Step-down from PPI to alternative treatment.

One RCT (593 patients with uninvestigated heartburn) reported that the highest percentage of heartburn-free periods were in patients receiving continuous lansoprazole 30 mg once daily for 20 weeks (82%). Corresponding rates were 66% for continuous ranitidine (150 mg twice daily for 20 weeks), 74% for 'step-up' from ranitidine 150 mg twice daily for 8 weeks followed by lansoprazole 30 mg daily for 12 weeks, and 67% for 'step-down' from lansoprazole 30 mg once daily for 8 weeks followed by ranitidine 150 mg twice daily for 12 weeks (P<0.01 for each comparison versus continuous lansoprazole).

Non-randomised studies.

Non-randomised studies reported that some patients with EE can achieve remission with PPI taken on alternate days or less often; the rates of remission on these reduced-dose regimens ranged from 26 to 79.5%.

Further details of these studies were reported in the review.

Authors’ conclusions
Evidence supports on-demand PPI treatment for patients with ENRD, but there is less support for on-demand treatment for patients with EE.

CRD commentary
The review addressed a clear question that was defined in terms of the participants, intervention and study design; the criteria for study design were broad and the inclusion criteria for outcomes were not defined. The lack of inclusion criteria for the outcomes raised the possibility of the reporting of selected outcomes. Two databases were searched and attempts were made to minimise publication and language bias. Methods were used to minimise reviewer errors and bias in the selection of studies, but it was not clear whether similar steps were taken in the data extraction and validity assessment processes. Only the validity of the RCTs was assessed; this was done using an established checklist. The outcomes were generally not defined and the validity of methods used to assess them was neither reported nor discussed.

The methods used to group the studies were appropriate, as was the use of a narrative synthesis. However, statements about results from individual studies were made without consistent presentation of supporting data and levels of statistical significance; this means it was not possible to verify the reported results. Incomplete reporting of review methods and limited information about study outcomes and results make the reliability of the review’s conclusions uncertain.

Implications of the review for practice and research
Practice: The authors stated that a step-down to no-treatment may be relevant for patients with ENRD but that patients may find this less acceptable.

Research: The authors stated that it is worthwhile considering trials of on-demand PPI treatment for patients with ENRD, and step-down from a PPI to no therapy in ENRD patients who initially experience a good symptomatic response to once daily PPI treatment.
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