

# Medical treatments for the maintenance therapy of reflux oesophagitis and endoscopic negative reflux disease (Review)

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[Intervention Review]

# Medical treatments for the maintenance therapy of reflux oesophagitis and endoscopic negative reflux disease

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## ABSTRACT

### Background

Gastro-oesophageal reflux disease (GORD) - reflux of stomach contents +/- bile into the oesophagus causing symptoms such as heartburn and acid reflux - is a common relapsing and remitting disease which often requires long-term maintenance therapy. Patients with GORD may have oesophagitis (inflammation of the oesophagus) or a normal endoscopy (endoscopy negative reflux disease or ENRD).

### Objectives

To assess the effects of continuous maintenance therapy in adults with GORD (both ENRD and healed oesophagitis).

### Search strategy

We searched Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 2, 2003), MEDLINE (1966 to 2003), EMBASE (1980 to 2003), CINAHL (1982-2003), and the National Research Register (Issue 2, 2003) and reference lists of articles. We also contacted manufacturers and researchers in the field.

### Selection criteria

Randomised controlled studies comparing PPIs, H2RAs, prokinetics, sucralfate and combinations either in comparison to another treatment regimen or to placebo in adults with reflux oesophagitis and ENRD.

### Data collection and analysis

One author extracted data from included trials and a second author carried out an unblinded check. Two authors independently assessed trial quality. Study authors were contacted for additional information.

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## Main results

Maintenance of patients with healed oesophagitis:

For a healing dose of PPI (generally the standard dose given by the manufacturer) versus placebo, the relative risk (RR) for oesophagitis relapse was 0.26 (95% confidence interval (CI) 0.19 to 0.36); versus H2RAs the RR was 0.36 (95% CI 0.28 to 0.46) and versus maintenance PPIs the RR was 0.63 (95% CI 0.55 to 0.73). However overall adverse effects were also more common and headaches were more common when comparing healing PPIs to H2RAs.

For a maintenance dose of PPI (half of the standard dose) versus placebo, the RR for oesophagitis relapse was 0.46 (95% CI 0.38 to 0.57) and versus H2RAs the RR was 0.57 (95% CI 0.47 to 0.69). Overall adverse effects were more common.

H2RAs were of marginal help but beneficial for symptomatic relief. Prokinetics and sucralfate were also more effective than placebo.

For ENRD patients:

Limited data with one RCT showed benefit for omeprazole 10 mg once daily over placebo (RR 0.4; 95% CI 0.29 to 0.53).

## Authors' conclusions

The findings in this review support the long-term treatment of oesophagitis to prevent relapse, both endoscopically and symptomatically. Healing doses of PPIs are more effective than all other therapies, although there is an increase in overall adverse effects compared to placebo, and headache occurrence compared to H2RAs. H2RAs prevent relapse more effectively than placebo, demonstrating a role for PPI-intolerant patients. Prokinetics and sucralfate both show benefit over placebo, but the former is no longer licenced. There is only limited data for ENRD.

## PLAIN LANGUAGE SUMMARY

### Medical treatments for the maintenance therapy of reflux oesophagitis and endoscopic negative reflux disease

Gastro-oesophageal reflux disease (GORD) is a common disease. GORD is usually due to acid and bile refluxing through the lower oesophageal sphincter and produces symptoms of heartburn, acid regurgitation, and less commonly chest and abdominal pain. The main treatments available concentrate on reducing acid secretion by proton pump inhibitors (PPIs) and H2 receptor antagonists (H2RAs), increasing the pressure at the lower oesophageal sphincter, enhancing gastric emptying with prokinetics and protecting mucosa from acid damage with sucralfate.

This review is a systematic review of randomised controlled trials examining the efficacy of continuous PPIs, H2RAs, prokinetic therapy and sucralfate in the maintenance therapy of reflux oesophagitis and endoscopy negative reflux disease. While intermittent or 'on-demand' therapy is increasingly being used, it is not covered by the scope of this review.

The findings of this review support the long-term treatment of oesophagitis to prevent relapse. Healing doses of PPIs are more effective than all other therapies, although there is an increase in overall adverse effects compared to placebo, and headache occurrence compared to H2RAs. H2RAs prevent relapse more effectively than placebo, demonstrating a role for PPI-intolerant patients. Prokinetics and sucralfate both show benefit over placebo, but the former is no longer licenced.

## BACKGROUND

Gastro-oesophageal reflux disease (GORD) is a common disease with an estimated prevalence of 20% in the adult American population (Sonnenberg 1999) and similar rates in Europe.

GORD is primarily attributable to acid and bile refluxing through the lower oesophageal sphincter (Armstrong 1999) and produces symptoms of heartburn, acid regurgitation, and less commonly chest and abdominal pain. The main treatments available concentrate on reducing acid secretion by proton pump inhibitors (PPIs)

and H2 receptor antagonists (H2RAs), increasing the pressure at the lower oesophageal sphincter, enhancing gastric emptying with prokinetics and protecting mucosa from acid damage with sucralfate.

Endoscopic examination is a common investigation for patients with GORD (Navaratham 1998). When endoscopy is undertaken a majority of patients have normal findings (endoscopy negative reflux disease or ENRD) with the remainder having oesophageal inflammation (oesophagitis).

The efficacy of medical therapy in acute management of oesophagitis has been the subject of other reviews and ENRD acute management has been evaluated in a previous Cochrane Review (van Pinxteren 2000). GORD is a chronic relapsing condition with significant impact on quality of life (Scott 1999). GORD symptoms recur rapidly on discontinuation of therapy therefore maintenance therapy is central to management of the condition (Williams 1997). There are currently only limited systematic reviews assessing maintenance therapy in the treatment of oesophagitis and none assessing ENRD.

GORD affects a significant number of patients who present for treatment and place a burden on healthcare budgets (Chiba 1997). Primary and secondary care physicians are faced with a variety of treatment options. Randomised controlled trials suggest that PPIs are the most effective acute healing treatment (Earnest 1999) but the actual relative efficacy of each drug in the maintenance therapy for reflux oesophagitis and ENRD is uncertain. An accurate assessment of this would inform clinical decision making. Efficacy is not the only aspect of the decision making process as cost of therapy also needs to be considered (Dent 1999). Nevertheless, a more precise estimate of relative efficacy would help establish the most cost-effective therapy for maintenance of reflux oesophagitis and ENRD patients.

This review is a systematic review of randomised controlled trials examining the efficacy of continuous PPIs, H2RAs, prokinetic therapy and sucralfate in the maintenance therapy of reflux oesophagitis and endoscopy negative reflux disease. While intermittent or 'on-demand' therapy is increasingly being used, it is not covered by the scope of this review.

## OBJECTIVES

- (1) To assess the efficacy of PPIs (at different doses), H2RAs, prokinetic therapy, sucralfate and combinations compared to each other and placebo in preventing relapse of mucosal inflammation in patients with oesophagitis.
- (2) To assess the efficacy of PPIs (at different doses), H2RAs, prokinetic therapy, sucralfate and combinations compared to each other and placebo in and preventing relapse of symptoms in patients with ENRD and oesophagitis.

- (3) To compare the incidence of adverse effects associated with the different treatments.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomised controlled trials assessing maintenance therapy of reflux oesophagitis and ENRD. Those studies assessing patients with 'complicated reflux disease' (i.e. those with oesophageal strictures or Barrett's oesophagus) were excluded.

#### Types of participants

All patients were adults who had had an endoscopy. In the case of ENRD, the main presenting symptoms were heartburn and/or acid reflux. Patients with reflux oesophagitis at endoscopy (mucosal inflammation and/or mucosal breaks of the oesophagus) required a repeat endoscopy to demonstrate healing after a course of therapy before entering into the maintenance phase of the trial. Any recognised grading of oesophagitis was acceptable and even if the oesophagitis was mild, patients were considered to have oesophagitis, rather than ENRD.

#### Types of interventions

The tested drug had to fall within the following drug classes a-d, the comparison regimen was also one of a-e. (Combinations of these were admissible for either arm).

- (1) PPIs: esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole.

We defined healing dose of a PPI as the manufacturers standard dose of drug (i.e. omeprazole 20mg, lansoprazole 30mg, pantoprazole 40mg and rabeprazole 20mg all once daily) whilst maintenance therapy was half this dose (i.e. omeprazole 10mg, lansoprazole 15mg, pantoprazole 20mg, rabeprazole 10mg). The exception was esomeprazole which is an S-enantiomer of omeprazole (a racemic mixture of S and R enantiomers). As esomeprazole 20mg should be at least as effective as omeprazole 20mg we defined a healing dose of esomeprazole as 20mg once daily and a maintenance dose as 10mg daily. This is half the manufacturers standard dose but this decision was taken to reduce heterogeneity between trials by keeping the same chemical entity at the same dose.) Double dose was defined as double the standard dose (i.e. omeprazole 40mg, esomeprazole 40mg).

- (2) H2RAs: cimetidine, famotidine, nizatidine, ranitidine (where results from different doses were pooled).
- (3) Prokinetic therapy: cisapride, domperidone, metoclopramide.

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