Review: Proton-pump inhibitor therapy reduces symptoms in nonulcer dyspepsia better than placebo

Moayyedi P, Delaney BC, Vakil N, Forman D, Talley NJ. **The efficacy of proton pump inhibitors in nonulcer dyspepsia: a systematic review and economic analysis.** Gastroenterology. 2004;127:1329-37.

QUESTION

In patients with nonulcer dyspepsia (NUD), is proton-pump inhibitor (PPI) therapy better than placebo for reducing dyspepsia symptoms?

METHODS

Data sources: Studies were identified by searching MEDLINE (1966 to September 2002), EMBASE/Excerpta Medica (1988 to September 2002), CINAHL (1982 to September 2002), Cochrane Controlled Trials Register (September 2002), and SIGLE; hand-searching general medical and major gastroenterology journals; and contacting pharmaceutical companies and experts in the field for unpublished studies.

Study selection and assessment: Studies in any language were selected if they were randomized controlled trials (RCTs) that compared PPI therapy with placebo, H_2-receptor antagonists, prokinetic therapy, antacids, or mucosal protection agents (excluding *Helicobacter pylori* eradication therapy), and assessed symptoms of dyspepsia as an outcome in patients who fulfilled Rome or Working Party definitions and had negative findings at endoscopy (hiatal hernia, < 5 gastric erosions, or mild duodenitis was permitted). Study quality was assessed for method of randomization, allocation concealment, and blinding of patients and investigators.

Outcomes: Relief of dyspepsia symptoms and incremental cost-effectiveness of PPI therapy compared with over-the-counter (OTC) antacids from a health service perspective. Costs were in 2004 U.S. dollars with no discounting of costs or effects.

MAIN RESULTS

8 RCTs (n = 3293) met the selection criteria. PPIs evaluated were omeprazole (5 RCTs) and lansoprazole (3 RCTs). Adequate randomization was done in 6 RCTs, concealment in 3 RCTs, and blinding in 4 RCTs. More patients who received PPI therapy had relief of dyspepsia than did those who received placebo (Table). Groups did not differ for relief of dyspepsia in 2 RCTs that compared PPIs with H_2-receptor antagonists (relative risk 0.93, 95% CI 0.84 to 1.02). From a health services perspective, incremental cost-effectiveness ratios for PPI therapy compared with OTC antacids were $278/mo free from dyspepsia at managed care PPI prices ($90/mo) and $57/mo at OTC PPI prices ($20/mo). If consumers are willing to pay $94/mo for freedom from dyspepsia, a 95% probability exists that OTC PPI therapy is cost-effective.

CONCLUSIONS

In patients with nonulcer dyspepsia, proton-pump inhibitor (PPI) therapy is better than placebo for relieving dyspepsia. PPI therapy is cost-effective at over-the-counter prices.

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Proton-pump inhibitors (PPIs) vs placebo for nonulcer dyspepsia at 2 to 8 weeks*

Outcome	Number of trials (*n*)	Weighted event rates		RBI (95% CI)	NNT (CI)
		PPI	Placebo		
Dyspepsia symptom relief	8 (3293)	33%	23%	14% (5 to 22)	9 (5 to 25)

*Abbreviations defined in Glossary; RBI, NNT, and CI calculated from data in article using a random-effects model.

COMMENTARY

Diagnosis of NUD requires a normal endoscopy result, but this is poorly handled in the literature. Before having endoscopy, many patients take acid-suppressive therapy, which can heal ulcers and erosions. Although clinical trials often exclude the use of such medication for 2 to 4 weeks before enrollment, it can take longer for esophagitis or ulcers to recur. Overlap between gastroesophageal reflux disease and dyspepsia is also a recognized problem because many patients with dyspepsia have heartburn as well (1).

Given the the proven efficacy of PPIs and H_2-receptor antagonists in upper-gastrointestinal disorders, it is reasonable to test their efficacy in NUD. However, clinical trials in NUD are difficult to do and strong evidence shows that the quality of study design affects the results (2). Recommendations for trial design will be updated next year by the ROME Working Party (3).

In the review by Moayyedi and colleagues, PPI therapy was superior to placebo for reducing symptoms of NUD (response rate 33% vs 23%, P = 0.003). Not surprisingly, associated heartburn was a predictor of response. Although most studies included in the meta-analysis were high-quality, the study by Blum and colleagues (which contributed 16% of the weight) was weak because the main outcome measure was poorly defined and investigators were aware of *H. pylori* status. Although heterogeneity of trials in the review was documented, its source was unclear. Of note, the placebo response rate was lowest in trials with absence of symptoms as the endpoint. The economic analysis was well-done, but none of the trials were designed to address cost-effectiveness of PPIs. Ultimately, the criterion for cost-effectiveness is the willingness of patients or society to pay.

Given the lack of better alternatives, it is reasonable to give patients with NUD a 4- to 8-week trial of PPI therapy to document whether symptoms are acid-sensitive.

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