Review: Proton-pump inhibitors alleviate symptoms of functional (nonulcer) dyspepsia but may not be better than H_2-antagonists

Shiau JY, Shukla VK, Dubé C. **The efficacy of proton pump inhibitors in adults with functional dyspepsia.** Technology Report No. 22. Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA); 2002. www.ccohta.ca.

QUESTION

In patients with functional dyspepsia (nonulcer dyspepsia [NUD]), are proton-pump inhibitors (PPIs) more effective than placebo, prokinetics, or H_2-antagonists for reducing symptoms?

DATA SOURCES

Studies were identified by searching MEDLINE, HealthSTAR, EMBASE/Excerpta Medica, PASCAL, SCISEARCH, and the Cochrane Controlled Trials Register; scanning the references of retrieved articles; hand searching issues of *Gastroenterology* and *Gut* from January 1995; and contacting pharmaceutical companies for unpublished studies.

STUDY SELECTION

Studies in any language were selected if they were randomized controlled trials (RCTs) that compared PPIs with placebo, prokinetics, or H_2-antagonists in adults (≥ 18 y of age) with NUD. Studies in which patients had biliary tract or gastroesophageal reflux disease, gastroparesis, lactose intolerance, malabsorption, parasitic infections, or preious eradication therapy for *Helicobacter pylori* were excluded.

DATA EXTRACTION

2 investigators independently extracted data on study quality, design, patient characteristics, dosages, treatment period, and outcomes. The primary outcome was the proportion of patients with no symptoms (excellent) or mild symptoms (good) of NUD. Secondary outcomes included freedom from individual symptoms of NUD, subgroup analysis in patients positive for *H. pylori*, and side effects.

MAIN RESULTS

6 RCTs (3 published studies and 3 abstracts) (n = 2368) met the selection criteria. All 6 trials compared a PPI with placebo. More patients who received PPIs had an excellent outcome or an excellent or good outcome than did patients who received placebo (Table). 1 of the 6 trials compared PPIs with H_2-antagonists. The groups did not differ for an excellent outcome or for an excellent or good outcome (Table). No trials comparing PPIs with prokinetics were identified. In 3 trials in which data on patients with *H. pylori* were available, PPIs were more effective than placebo (good or excellent outcome odds ratio [OR] 1.78, 95% CI 1.09 to 2.91). 3 trials that reported side effects showed no difference between PPIs and placebo (OR 0.97, CI 0.68 to 1.39).

CONCLUSION

In patients with functional dyspepsia, proton-pump inhibitors are more effective than placebo for reducing symptoms but may not be more effective than H_2-antagonists.

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Proton-pump inhibitors (PPIs) vs placebo or H_2-antagonists for functional dyspepsia*

Outcomes at 2 to 4 wk	Number of trials	Comparison	Weighted event rates	RBI (95% CI)	NNT (CI)
Excellent	4	PPI vs placebo	39% vs 26%	48% (30 to 68)	8 (7 to 12)
Good or excellent	6	PPI vs placebo	60% vs 49%	21% (12 to 31)	10 (6 to 16)
Excellent	1	PPI vs H_2-antagonists	31% vs 25%†	25% (–5.6 to 67)	Not significant
Good or excellent	1	PPI vs H_2-antagonists	60% vs 60%†	0.3% (–12 to 16)	Not significant

*Excellent = no symptoms; good = mild symptoms of dyspepsia. Abbreviations defined in Glossary; RBI, NNT, and CI calculated from data in article using fixed effects.
†Event rates not weighted.

COMMENTARY

Dyspepsia is a common and vexing problem. PPI prescriptions have increased dramatically. Their total cost now exceeds that of all other agents for dyspepsia combined, despite a lack of direct evidence of superiority (1).

The systematic review by Shiau and colleagues included 6 RCTs of PPIs for NUD. 3 were abstracts from the mid-1990s, all rated as low quality, for which detailed methods were not available. The efficacy of PPIs in this review was largely driven by 1 high-quality international trial of > 1200 patients (2).

The Rome II consensus panel defined NUD as symptoms lasting ≥ 12 weeks without evidence of organic disease, including at endoscopy (3). Case definition, symptom duration, and exclusion criteria varied substantially among the 6 trials. This may render the pooled estimate of effect less trustworthy, despite statistical homogeneity.

The authors report possible publication bias for the "excellent" outcome, which suggests that negative trials may have been missed. Readers should interpret results for this outcome with caution.

Although PPIs are more potent healers of ulcers, evidence that they are superior to other agents for NUD is indirect at best. The only trial to compare a PPI and an H_2-antagonist directly found no difference.

An issue not addressed in this review is the role of *H. pylori* eradication for NUD. Growing evidence shows that eradication can modestly improve symptoms in NUD (4).

Because many patients require long-term treatment for NUD, clinicians should seek the most cost-effective options. It seems that a "step-up" strategy for NUD, starting with antacids or H_2-antagonists may be justified until comparative trials and cost-effectiveness analyses are done. PPIs can be reserved for patients who do not respond to initial therapy.

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