Effects of Proton-Pump Inhibitors on Functional Dyspepsia: A Meta-analysis of Randomized Placebo-Controlled Trials

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Background & Aims: The aim of this study was to assess systematically the efficacy of proton pump inhibitors (PPIs) in the treatment of functional dyspepsia compared with placebo and to determine if any difference in the response exists between symptom subgroups of functional dyspepsia. Methods: A literature search was performed through September 2005 in PubMed, Medline, Embase, CINAHL, and Cochrane databases to include randomized, double-blind, placebo-controlled trials evaluating the efficacy of PPIs for the treatment of functional dyspepsia. Relative risk (RR) and relative risk reduction (RRR) and 95% confidence intervals (CI) were calculated under a random-effects model. Results: Seven studies with a total of 3725 patients were identified. PPIs were found to be more effective than placebo for reducing symptoms in patients with functional dyspepsia (RRR, 10.3%; 95% CI, 2.7%–17.3%). The estimated number needed to treat is 14.6 (95% CI, 8.7–57.1). When stratified analyses were performed, a significant difference in the efficacy was observed only in patients with ulcer-like (RRR, 12.8%; 95% CI, 7.2%–18.1%) and reflux-like dyspepsia (RRR, 19.7%; 95% CI, 1.8%–34.3%), but not in those with dysmotility-like (RRR, 5.1%; 95% CI, −10.9% to 18.7%) and unspecified dyspepsia (RRR, −8.0%; 95% CI, −23.7% to 5.6%). The effect of H pylori on the efficacy of PPIs remains unclear. Significant heterogeneity among studies was found for the overall analysis, dysmotility-like dyspepsia, H pylori–negative subgroup, and different dose subgroups. Conclusions: PPIs are more effective than placebo for the management of patients with ulcer-like and reflux-like functional dyspepsia.

F functional, or nonulcer, dyspepsia (NUD) is defined as persistent or recurrent pain or discomfort centered in the upper abdomen for more than 12 weeks in the preceding 12 months with no evidence of an organic disease that is likely to explain the symptoms.1 NUD has a significant adverse impact on patients’ quality of life and economic consequences.2,3 However, because the pathophysiology of functional dyspepsia is understood poorly, symptom control is currently the mainstream of management. Eradication of Helicobacter pylori and acid suppression are used commonly in the treatment of functional dyspepsia, although conflicting results regarding their efficacy have been reported in the literature.4–11 Most studies have shown that proton pump inhibitors (PPIs) are significantly more effective than placebo for treating patients with functional dyspepsia.4–10 However, in a recent large, well-designed, randomized study conducted in Hong Kong, Wong et al11 reported that lansoprazole 15 mg or 30 mg once daily given for 4 weeks showed similar efficacy to placebo for treating patients with functional dyspepsia. Thus, it is not clear to the practicing physicians whether PPIs should be recommended for use in controlling symptoms in patients with functional dyspepsia.

Functional dyspepsia can be divided into 4 symptom groups: ulcer-like, dysmotility-like, reflux-like, and unspecified dyspepsia.12 Because patients with reflux-like dyspepsia are likely to have gastroesophageal reflux disease, they therefore are no longer considered as functional dyspepsia according to the Rome II criteria.1 Symptom overlap is very common in patients with functional dyspepsia12,13 and the efficacy of treatments targeting specific symptoms has not been well studied. Although our comprehensive search identified 2 published systematic reviews evaluating the effect of PPIs in NUD,10,14 they suffered several serious methodologic flaws such as an incomplete literature search, inclusion of duplicate publications, and no stratified analysis by dose of PPIs or different types of symptoms.10,14 A more recent, well-conducted, systematic review shows that PPIs have a small but statistically significant effect on symptoms of NUD.15 However, this article included a study16 that was part of a multinational trial16 and missed a study that met the inclusion criteria.17

Therefore, we performed this meta-analysis to evaluate the efficacy of PPIs for treating patients with functional dyspepsia in comparison with placebo. We also assessed if there was any difference in the response to PPI treatment between patients in different symptom subgroups.

Materials and Methods

Literature Search

A comprehensive computerized literature search was performed using the PubMed, Medline, Embase, CINAHL, Cochrane Controlled Trials Register databases for clinical

Abbreviations used in this paper: CI, confidence interval; NNT, number needed to treat; NUD, nonulcer dyspepsia; PPI, proton pump inhibitor; RR, relative risk; RRR, relative risk reduction.
trials published through September 2005 without any language restriction. The following search terms as either MeSH terms or text words were used in various combinations: non-ulcer, functional, dyspepsia, NUD, in combination with proton pump inhibitors, PPI, and the name of each respective drug (omeprazole, lansoprazole, pantoprazole, rabeprazole, and esomeprazole). The search was limited to clinical trials only. Meeting abstracts were searched from CD-ROMs of major gastrointestinal meetings (American Digestive Disease Week, American College of Gastroenterology, World Congress of Gastroenterology, and United European Gastroenterology Week) held in the past 8 years using the earlier-described search terms. The titles and abstracts of all potentially relevant studies were screened for their relevance before retrieval of full articles. Full articles also were scrutinized for relevance if the title and abstract were ambiguous. A fully recursive search also was performed from the reference lists of all retrieved articles to ensure a complete and comprehensive search of the published literature. All searches were conducted independently by 3 reviewers (W.H.W., G.F.Z., and J.Q.H.) and their search results were combined.

Study Selection

Studies that met the following criteria were included: (1) randomized, double-blind, placebo-controlled trials evaluating the efficacy of PPIs for treating patients with functional dyspepsia; (2) functional dyspepsia defined as persistent or recurrent dyspepsia with no evidence of organic disease to explain the patient’s symptoms; (3) studies performed in an adult population; and (4) studies that reported information about the number of patients treated and the number of patients with improvement.

Studies in which patients had gastroesophageal reflux disease, peptic ulcer disease, nonsteroidal anti-inflammatory drug-related gastropathy, irritable bowel syndrome, biliary tract disease, or pancreatic disease were excluded. We also excluded duplicate publications or studies that did not provide raw data, or that included patients who received a combination of treatments.

Data Extraction

Data were extracted from each study by 2 reviewers (W.H.W. and G.F.Z.) independently and entered into a computerized database. Any differences were resolved by discussion to reach consensus between the authors. The information retrieved covered study design, publication type, patient characteristics (age, sex, history of dyspepsia, dyspepsia symptoms, H pylori status), diagnostic criteria, treatment regimen (drug, dose, duration), outcome measures, and study outcomes. Data on the number of patients showing improvement and the status of H pylori infection before and after treatment were extracted according to intention-to-treat criteria. If possible, data also were extracted by subgroups of symptoms (ie, ulcer-like, reflux-like, dysmotility-like, and unspecified dyspepsia).

Quality Assessment

Study quality was assessed by a series of validity criteria, including study design, level of blinding, method of randomization, diagnostic criteria of dyspepsia, baseline characteristics, patient compliance, and outcome measures, and analysis by intention to treat criteria. Any discrepancies in quality assessment were resolved by consensus among the authors. No quality score was assigned to any study to avoid possible introduction of subjectivity by the authors. Instead, we used these validity criteria to rank the studies (Table 1).

Statistical Analysis

For the meta-analysis the terms no symptoms, no symptoms for further management, and improvement on gastrointestinal symptom rating scale after the completion of treatment were defined as treatment success. Relative risk (RR) and relative risk reduction (RRR) ([1 − RR] × 100%) together with 95% confidence intervals (CIs) were calculated to estimate the efficacy of intervention using raw data from selected studies and then statistically combined under a random-effects model.18 The number needed to treat (NNT) also was calculated by evaluating the mean proportion of patients with continued dyspepsia in the placebo groups of the trials (P2). The NNT = 1/(P2 × [1 − RR]) and the 95% CIs were obtained from the 95% CI of the RR.

Meta-regression was performed to explore the influence of the following factors on treatment effects: (1) the dose of PPI, (2) the proportion of patients with predominant symptoms, (3) the proportion of patients with H pylori infection, and (4) the duration of treatment. A standard dose of PPI included omeprazole 20 mg/day and lansoprazole 30 mg/day, and low-dose PPI was defined as omeprazole 10 mg/day and lansoprazole 15 mg/day. The data for different dyspepsia subgroups also were pooled to evaluate if there was any difference in the response to PPI treatment between patients in different symptom subgroups.

Statistical heterogeneity among studies was assessed using the Q value calculated from the Mantel-Haenszel method. In the presence of statistical heterogeneity, we searched for the sources of any possible clinically important heterogeneity (ie, methodologic or biological heterogeneity). We did not simply exclude outliers on the basis of statistical tests of heterogeneity. Furthermore, to exclude any possible influence of a single study, we performed a sensitivity analysis to evaluate whether the exclusion of any single study substantially altered the magnitude or statistical result of the summary estimate. The potential effect of any publication bias was assessed using a funnel plot of log RR vs precision of individual studies as suggested by Egger et al.19

All analyses were performed using Comprehensive Meta-analysis software (version 1.0.25, Biostat, Englewood, NJ).

Results

Literature Search and Study Selection

We identified a total of 716 citations with the computerized search and 398 meeting abstracts from the CD-ROMs of major gastrointestinal meetings. A manual search of the reference list of the retrieved articles yielded 1 additional study. Screening of the title and abstract of the publications identified 31 potentially relevant studies for full article retrieval. Of these, 7 studies met the inclusion criteria, and 24 studies subsequently were excluded for the following reasons: 8 studies evaluated patients with uninvestigated...
dyspepsia without endoscopy,22–29 7 studies had no placebo-controlled group,30–36 1 study was a follow-up study of patients receiving treatment for dyspepsia,37 1 study had no raw data,38 6 studies were duplicate publications,3 9–4 4and 1 study16 reported results that were used by a multinational trial. 4 When duplicate publications were found, we only included the article that provided the most comprehensive information.

### Study Characteristics and Quality

Of the 7 studies, 6 were published as full articles,4 – 6,11,17,20 and 1 was in abstract form.21 Four studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnostic method</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Treatment</th>
<th>No. of patients</th>
<th>Definition of symptom relief</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wong et al11</td>
<td>Endoscopy</td>
<td>Rome II criteria (at least 12 wk within the preceding 12 mo), symptoms in 2 weeks before endoscopy</td>
<td>Reflux symptoms without epigastric symptoms, RE, PU, erosive change in stomach or duodenum, alcohol, history of PU and GERD, NSAID, severe illness, IBS, constipation</td>
<td>LAN 30 mg, 4 wk; LAN 15 mg, 4 wk</td>
<td>453</td>
<td>Complete relief at the last 3 days of treatment</td>
</tr>
<tr>
<td>Talley et al4</td>
<td>Endoscopy &lt;5 gastric erosion</td>
<td>At least 1 of the 3 days before randomization, 1-mo history of dyspeptic symptoms, symptoms occur on &gt;25% of days during that month</td>
<td>Reflux symptoms without epigastric symptoms, RE, PU, erosive change in stomach/duodenum, upper-GI surgery, alcohol, history of PU and GERD, IBS, severe illness, alarm symptom, constipation</td>
<td>OME 20 mg, 4 wk; OME 10 mg, 4 wk</td>
<td>1248</td>
<td>Complete relief at the last 3 days of treatment</td>
</tr>
<tr>
<td>Peura et al20</td>
<td>Endoscopy &lt;5 gastric erosion</td>
<td>Symptoms for at least 30% of the days during the pretreatment, 3 months history of dyspeptic symptoms</td>
<td>Predominant symptoms indicating GERD or IBS, PU, &gt;5 gastric erosions</td>
<td>LAN 30 mg, 8 wk; LAN 15 mg, 8 wk</td>
<td>921</td>
<td>Complete relief during the 3 days before visit</td>
</tr>
<tr>
<td>Bolling-Sternevald et al17</td>
<td>Endoscopy &lt;5 gastric erosion, 24-h pH monitoring</td>
<td>At least 3 days in the run-in week symptoms for at least 1 month</td>
<td>Predominant symptoms indicating GERD or IBS, history of PU and GERD, upper-GI surgery, alarm symptom, NSAID</td>
<td>OME 20 mg, 2 wk</td>
<td>196</td>
<td>Complete relief at the last days of treatment</td>
</tr>
<tr>
<td>Blum et al6</td>
<td>Endoscopy &lt;10 gastric erosion Sonography, CT</td>
<td>At least 3 days in the run-in week symptoms for at least 1 month</td>
<td>Reflux symptoms without concomitant epigastric symptoms, IBS, RE, PU, alcohol abdominal surgery, alarm symptom</td>
<td>OME 20 mg, 2 wk; OME 10 mg, 2 wk</td>
<td>598</td>
<td>No symptom for further management</td>
</tr>
<tr>
<td>Gerson and Triadafilopoulos17</td>
<td>Endoscopy</td>
<td>Rome II criteria (at least 12 wk within the preceding 12 mo), H pylori negative, lack of symptom relief on H2-blocker</td>
<td>RE, predominant GERD symptoms, malignancy, NSAID</td>
<td>OME 20 mg, 4 wk</td>
<td>40</td>
<td>Improvement on GSRS score between baseline and 4 weeks</td>
</tr>
<tr>
<td>Hengels21</td>
<td>Endoscopy sonography</td>
<td>Symptoms for at least 1 week</td>
<td>Unknown</td>
<td>LAN 15 mg, 2 wk</td>
<td>269</td>
<td>No symptoms during the last 5 days of treatment</td>
</tr>
</tbody>
</table>

**Table 1. Characteristics of Studies Selected for Meta-Analysis**

NOTE. Studies were ranked according to their study quality.

RE, reflux esophagitis; PU, peptic ulcer; LAN, lansoprazole; GERD, gastroesophageal reflux disease; NSAID, nonsteroidal anti-inflammatory drug; IBS, irritable bowel syndrome; OME, omeprazole; GI, gastrointestinal; GSRS, gastrointestinal symptom rating.
Table 2. Statistical Results Comparing PPIs With Placebo in Subgroups of Functional Dyspepsia Under Random-Effects Model

<table>
<thead>
<tr>
<th>Groups</th>
<th>No. of studies</th>
<th>No. of patients</th>
<th>RR; 95% CI</th>
<th>RRR (%); 95% CI</th>
<th>NNT; 95% CI</th>
<th>Test of heterogeneity</th>
<th>Q value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulcer-like</td>
<td>3</td>
<td>1405</td>
<td>0.87; 0.82–0.93</td>
<td>12.8; 7.2–18.1</td>
<td>10.9; 7.6–19.5</td>
<td>1.746</td>
<td>.88</td>
<td></td>
</tr>
<tr>
<td>Reflux-like</td>
<td>3</td>
<td>380</td>
<td>0.80; 0.66–0.98</td>
<td>19.7; 1.8–34.3</td>
<td>6.8; 3.9–74.1</td>
<td>9.26</td>
<td>.10</td>
<td></td>
</tr>
<tr>
<td>Dysmotility-like</td>
<td>3</td>
<td>583</td>
<td>0.95; 0.81–1.11</td>
<td>5.1; −10.9 to 18.7</td>
<td>27.1; −12.7 to 7.4</td>
<td>13.47</td>
<td>.04</td>
<td></td>
</tr>
<tr>
<td>Dysmotility-like({}^a)</td>
<td>2</td>
<td>339</td>
<td>0.84; 0.69–1.02</td>
<td>15.8; −2.2 to 30.6</td>
<td>8.5; −68.0 to 4.4</td>
<td>5.30</td>
<td>.15</td>
<td></td>
</tr>
<tr>
<td>Unspecified</td>
<td>4</td>
<td>289</td>
<td>0.08; 0.94–1.24</td>
<td>−8.0; −23.7 to 5.6</td>
<td>−18.8; −6.3 to 26.9</td>
<td>2.75</td>
<td>.84</td>
<td></td>
</tr>
</tbody>
</table>

\({}^a\)Excluding one heterogeneous study.\(^{11}\)

Comparison of omeprazole\(^{4–6,17}\) with placebo, and 3 compared lansoprazole\(^{11,20,21}\) with placebo. Six studies recruited patients with symptoms for at least 1 or 3 months.\(^{4–6,11,17,20}\) and 1 study did not provide information about patients’ previous history of functional dyspepsia.\(^{21}\) The Rome II criteria were used to select patients by 2 studies.\(^{11,17}\) In all studies, endoscopy was performed before the enrollment of patients. Patients with a history of peptic ulcer disease were excluded in 5 studies.\(^{4–6,11,20}\) Gastroesophageal reflux disease was considered an exclusion criterion in 6 studies.\(^{4–6,11,17,20}\) However, this information was not available from 1 abstract (Table 1).\(^{21}\) All studies provided information about \(H\) pylori assessment.\(^{4–6,11,17,20,21}\) Detailed information on subgroups of symptoms also was provided by 4 studies.\(^{4,11,17,20}\)

All studies were performed in a double-blind fashion. Computer-generated randomization was reported in 4 studies,\(^{5,6,11,20}\) and this information was not given in the remaining 3 (Table 1).\(^{5,6,11,17,20}\) Demographic information was reported in 6 studies.\(^{4–6,11,17,20}\) The mean patient age was 43.1 ± 2.1 years (±SEM) and 37% were male. The duration of medical therapy in the studies varied among 2 weeks,\(^{5,6,11,17,20}\) 4 weeks,\(^{4,11,17}\) and 8 weeks (Table 2).\(^{20}\) With respect to the outcomes, no symptoms during the last 3 days of treatment was considered as complete relief by 3 studies,\(^{4,11,20}\) whereas a different definition of symptom relief was used in the remaining 4 studies.\(^{5,6,11,17,20}\)

**Overall Analysis**

There were a total of 7 studies consisting of 3725 patients (PPI, 2387; placebo, 1338). There was a modest but statistically significant difference in symptom relief in patients receiving PPIs (40.3%) compared with those given placebo (32.7%), yielding a RRR of 10.3% (95% CI, 2.7%–17.3%), test for heterogeneity, \(Q = 31.46, P = .0005\). The estimated NNT was 14.7 patients (95% CI, 9.5%–19.5%).

**Test for Heterogeneity and Sensitivity Analyses**

There was significant heterogeneity among the 7 included studies for the overall analysis (\(Q = 31.46, P = .0005\)). Meta-regression did not find any relationship between the estimated RRR of dyspeptic symptoms and the proportion of patients with predominant reflux-like symptoms (\(P = .101\)) and \(H\) pylori infection (\(P = .146\)), and the dose (\(P = .340\)) and duration of PPI treatment (\(P = .255\)). Therefore, any of these prespecified factors could explain the heterogeneity between trials.

No further heterogeneity (\(Q = 11.06, P = .20\)) was found after exclusion of the study by Wong et al,\(^{11}\) suggesting that the heterogeneity was caused by this study. Looking at the inclusion criteria, it can be seen that this large study included Chinese patients, who are known to have a relatively low prevalence of gastroesophageal reflux disease.\(^{45}\) No additional confounding factors such as study design, level of blinding, compliance of patient, and definition of outcomes were identified. Sensitivity analysis by excluding the data from the study by Wong et al\(^{11}\) showed no difference in the overall analysis (RRR, 14.7%; 95% CI, 9.5%–19.5%).

**Dose Effect**

A low dose of PPIs was compared with placebo in 5 studies involving 2418 patients,\(^{4–6,11,20,21}\) whereas standard-dose PPIs were used in 6 studies with a total of 2392 patients.\(^{4–6,11,17,20}\) There was a clear trend that both low-dose and standard-dose PPIs were superior to placebo for the treatment of functional dyspepsia (Figure 1). Meta-regression did not suggest that the dose of PPI influenced the estimated RRR of dyspeptic symptoms (\(P = .340\)). The individual and summary RRs and 95% CIs from the individual trials and combined estimates of low- and standard-dose PPIs are shown in Figure 1.

**Helicobacter pylori Infection**

A total of 1394 \(H\) pylori–positive patients from 6 studies were available for analysis.\(^{4–6,11,20,21}\) There was a significant reduction in dyspeptic symptoms in patients receiving PPIs compared with those given placebo, with a RRR of 13.3% (95% CI, 5.0%–20.9%; test for heterogeneity, \(Q = 14.45, P = .11\)). The NNT was estimated at 11.4 patients (95% CI, 7.2–30.2 patients). A total of 2284 \(H\) pylori–negative patients from 7 studies were analyzed.\(^{4–6,11,17,20,21}\) There was a trend toward PPIs being more effective than placebo for symptom improvement, although the difference was not statistically significant (RRR, 5.7%; 95% CI, −5.3% to 15.5%). Meta-regression did not indicate that the effect of PPIs on dyspeptic symptoms was associated with \(H\) pylori infection (\(P = .146\)).
Dyspepsia Subgroup

Four of the 7 studies provided raw data on the number of patients with ulcer-like, reflux-like, dysmotility-like, and unspecified dyspepsia according to the predominance of symptoms. One study was excluded from the analysis of ulcer-like, reflux-like, and dysmotility-like subgroups because of a small number of patients (n ≤ 2). PPIs were found to be more effective than placebo for reducing symptoms in patients with ulcer-like and reflux-like functional dyspepsia, with a RRR of 12.8% (95% CI, 7.2%–18.1%; test for heterogeneity, Q = 1.75; P = .88) and 19.7% (95% CI, 1.8%–34.3%; test for heterogeneity, Q = 9.26; P = .10), respectively. The NNT with PPIs to improve 1 case of dyspepsia was 10.9 (95% CI, 7.6–19.5) and 6.8 (95% CI, 3.9–74.1), respectively. The RRRs for dysmotility-like and unspecified subgroups were 5.1% (95% CI, −10.9% to 18.7%; test for heterogeneity, Q = 13.47; P = .04) and −8.0% (95% CI, −23.7% to 5.6%; test for heterogeneity, Q = 2.75; P = .84), respectively, indicating that PPIs were not superior to placebo for the treatment of dysmotility-like and unspecified dyspepsia.

Publication Bias

The funnel plots obtained by plotting the log RRs vs precision (1/SE) of individual studies was symmetric for overall and subgroup analyses, suggesting that there was no significant publication bias in this literature (data not shown).

Discussion

Our present meta-analysis shows that PPIs were significantly more effective than placebo for treating patients with functional dyspepsia, with a 10.3% reduction in the RR of dyspeptic symptoms and an NNT of 14.6 patients. This finding was consistent across different doses of PPIs and the patients’ status of H pylori infection.

Previous studies have shown that there was an extensive overlap among patients with different subgroups of functional dyspepsia. We found 4 studies that provided information on symptom subgroups. The combined analysis of these studies showed that, in patients with reflux-like and ulcer-like dyspepsia, the relative risk reduction of dyspepsia was significantly greater in patients receiving PPIs than those treated with placebo. However, no significant difference in the efficacy was observed between PPIs and placebo in patients with dysmotility-like and unspecified dyspepsia. These results have provided some evidence that gastric acid may play a role in the pathogenesis of ulcer-like or reflux-like functional dyspepsia and the results generated from the subgroup analysis of symptoms could have potentially clinical use for predicting patients’ response to the treatment.

It is possible that patients with reflux-predominant dyspepsia are actually those with gastroesophageal reflux disease because there is a considerable overlap in symptoms between functional dyspepsia and nonerosive or endoscopic-negative reflux disease. Although meta-regression found no significant relationship between the RRR of dyspeptic symptoms and the proportion of patients with reflux-predominant dyspepsia, there was a trend that the reported benefit of PPIs increased with the proportion of patients with reflux-like dyspepsia in the individual studies. Therefore, it
is conceivable that inclusion of patients with reflux-predominant dyspepsia might increase the difference in symptom relief between patients treated with PPIs and placebo. This might be the rationale why, in the Rome II criteria, reflux-like dyspepsia was excluded.1

There was statistically significant heterogeneity between studies. Although meta-regression did not suggest that the proportion of patients with predominant reflux-like symptoms and H pylori infection, and the dose and duration of PPI treatment, could explain the heterogeneity between trials, these factors still may be important modifiers of the efficacy of PPI in patients with functional dyspepsia. Based on the statistical heterogeneity identified in the overall analysis, we found that the study by Wong et al54 was responsible for all the heterogeneities identified. Further scrutiny revealed that this was a considerably large trial involving 453 patients, and Wong et al54 did not find any significant difference in symptom relief between patients receiving PPIs and those given placebo regardless of symptom subgroups. Three specific differences were found between this study and the others. First, this study was performed in Chinese patients, who are known to have a relatively low prevalence of gastroesophageal reflux disease.45 Second, the study population was a carefully selected cohort by a group of gastroenterologists,11 resulting in the exclusion of most patients with gastroesophageal reflux disease. In this study, approximately 4% of patients reported acid reflux symptoms as their predominant symptom and the majority of patients had dysmotility-like symptoms (54%) as their predominant symptom.11 Furthermore, a previous study revealed that patients seen by gastroenterologists responded better to placebo than those seeing general practitioners.4 In this study, a relatively higher placebo response rate also was found. Third, the Rome II criteria were used in this study to select patients.11 In the analysis of the effect of PPIs for the treatment of functional dyspepsia, the main concern is the admixture of patients with nonerosive gastroesophageal reflux disease because patients with nonerosive gastroesophageal reflux disease are known to respond to PPIs.48–50 Therefore, the observed efficacy of PPIs in functional dyspepsia actually may be the result of treating patients with nonerosive gastroesophageal reflux disease.16,51 However, this may not be the case in the study by Wong et al11 because of the adoption of the Rome II criteria for patient recruitment.

The role of H pylori infection in functional dyspepsia has long been a subject of controversy. Two meta-analyses have come to opposite conclusions regarding whether H pylori eradication leads to sustained symptom improvement in H pylori-infected patients with functional dyspepsia.52,53 A recent systematic review concluded that H pylori eradication benefits functional dyspepsia patients, but the effect size is likely to be small. The reason for the differences between studies may relate to the overall numbers of patients included in the analysis.54 Furthermore, there is evidence to show that a subset of patients with functional dyspepsia who are infected with H pylori have abnormal gastric acid secretion,55 suggesting a possible role of gastric acid in functional dyspepsia. Virulent strains of H pylori are associated with a higher prevalence of dyspeptic symptoms, especially in patients with epigastric pain.56 Therefore, it is reasonable to presume that this group of patients may respond better to PPI treatment than H pylori–negative patients with functional dyspepsia. However, in our meta-regression, we did not find that the variation in H pylori status was associated with the variation in the efficacy of PPI treatment. At least part of the reason for this may be because there were fewer studies included in the meta-regression. Although meta-regression is an extension to subgroup analyses that allows the effect of categorical characteristics to be investigated, and in principle allows the effects of multiple factors to be investigated simultaneously, it is believed that at least 10 studies in a meta-analysis should be available for each characteristic modeled to produce reliable results.57 Thus, no firm conclusions can be made because of concerns over the small sample size included in this study. The question of whether PPI treatment is more effective in H pylori–positive functional dyspepsia patients than those without the infection warrants further investigation in future randomized controlled trials.

As with meta-analysis in general, there were several limitations to our meta-analysis.58,59 First, to avoid publication bias, a phenomenon in which studies with positive results are more likely accepted for publication than those with negative results, we included both published studies and meeting abstracts in our search strategy. However, a potential publication bias could not be ruled out completely because 5 of the 7 studies included in the analysis had positive results.4–6,20,21 Because the funnel plots were symmetric for both the overall and subgroup analyses, any possible publication bias might not be significant if it exists. Second, the lack of consensus on the diagnosis of functional dyspepsia and the use of different outcome measurements of treatment has hampered us from comparing any difference in the efficacy of treatment between studies.60,61 A meta-analysis of studies with different inclusion criteria and different definitions of symptom relief may produce biases. As was indicated recently, the quality of trials included in a meta-analysis may have an impact on the efficacy estimates of treatment in functional dyspepsia.54 Third, different treatment durations were used in the included studies ranging from 2 to 8 weeks, and no follow-up data were reported after the treatment was stopped. Therefore, it was not clear whether symptoms would recur once the treatment was stopped. Because functional dyspepsia is a chronic relapsing disorder, future studies are needed to evaluate if the benefit of PPIs can last after treatment is stopped, or if intermittent or on-demand use of PPIs could be recommended.

In conclusion, by using the technique of meta-analysis, we found that PPIs were significantly more effective for controlling dyspeptic symptoms than placebo, especially in patients with ulcer-like and reflux-like dyspepsia. The estimated NNT for treatment of functional dyspepsia overall is approximately 15. The role of H pylori on the efficacy of PPIs in treating functional dyspepsia remains to be determined.

References


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