The Efficacy of Proton Pump Inhibitors in Nonulcer Dyspepsia: A Systematic Review and Economic Analysis

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Background & Aims: The evidence that proton pump inhibitor (PPI) therapy affects symptoms of nonulcer dyspepsia is conflicting. We conducted a systematic review to evaluate whether PPI therapy had any effect in nonulcer dyspepsia and constructed a health economic model to assess the cost-effectiveness of this approach.

Methods: Electronic searches were performed using the Cochrane Controlled Trials Register, MEDLINE, EMBASE, CINAHL, and SIGLE until September 2002. Dyspepsia outcomes were dichotomized into cured/improved versus same/worse. Results were incorporated into a Markov model comparing health service costs and benefits of PPI with antacid therapy over 1 year. Results: Eight trials were identified that compared PPI therapy with placebo in 3293 patients. The relative risk of remaining dyspeptic with PPI therapy versus placebo was .86 (95% confidence interval, .78–.95; P < .003, random-effects model) with a number needed to treat of 9 (95% confidence interval, 5–25). There was statistically significant heterogeneity between trials (heterogeneity 2 = 30.05; df = 7; P < .001). The PPI strategy would cost an extra $278/month free from dyspepsia if the drug cost $90/month. If a generic price of $19.99 is used, then a PPI strategy costs an extra $57/month free from dyspepsia. A third-party payer would be 95% certain that PPI therapy would be cost-effective, provided they were willing to pay $94/month free from dyspepsia. Conclusions: PPI therapy may be a cost-effective therapy in nonulcer dyspepsia, provided generic prices are used.

Proton pump inhibitors (PPIs) have become the most important drug class for the treatment of patients with gastroesophageal reflux disease.1 Approximately $2 billion is spent on PPI therapy each year in the United States, because gastroesophageal reflux disease is a common cause of upper gastrointestinal symptoms.2 The other common cause of upper gastrointestinal symptoms is nonulcer dyspepsia (NUD), which is the most frequent diagnosis reached after endoscopy.3 The cause of NUD is unclear, but it is likely to be multifactorial.4 The role of acid suppression in NUD is controversial,5 and randomized controlled trials of the efficacy of PPI therapy in NUD have given conflicting results.6,7 It is important to establish the efficacy of PPI therapy in NUD because these drugs can now be bought over the counter and this is likely to lead to their more indiscriminate use for any upper gastrointestinal symptom. We hypothesized that PPI therapy would have a modest effect in NUD and that this strategy would be a reasonable use of resources. We therefore conducted a systematic review using Cochrane Collaboration methodology8 of randomized controlled trials evaluating PPI therapy in NUD and constructed health economic models to evaluate the cost-effectiveness of this approach. Because PPI therapy is available over the counter, a variety of perspectives have been taken.

Patients and Methods

Systematic Review

Search strategy. Trials were identified from the Cochrane Controlled Trials Register (September 2002), MEDLINE (1966 to September 2002), EMBASE (1988 to September 2002), and CINAHL (1982 to September 2002), and the gray literature (eg, conference reports, technical reports, and dissertations) was searched using SIGLE. Details of the search strategy used for each database are published in the Cochrane Library.9 For example, for MEDLINE, patients with dyspepsia were identified with the medical subject heading and text term “dyspepsia” together with text words for symptoms of dyspepsia such as “indigestion,” “early adj5 satiety,” and “Symptom$ adj5 score$.” These references were combined using the set operator

Abbreviations used in this paper: CI, confidence interval; NUD, nonulcer dyspepsia; PPI, proton pump inhibitor; RR, relative risk.

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“AND” with studies that evaluated active or control intervention. These were identified with medical subject heading terms for omeprazole and proton pump together with text words for all PPIs, H$_2$-receptor antagonists, prokinetics, antacids, and mucosal protecting agents.

A recursive bibliography search of eligible randomized controlled trials and relevant review papers was conducted. Experts in the field of dyspepsia and pharmaceutical companies were contacted for unpublished materials. General medical and major gastroenterology journals were routinely scanned over the previous year to ensure that the most recent studies were included. Papers were considered regardless of language and publication status. Abstracts were only included when further details were available from the investigators.

**Assessment of eligibility and trial quality.** Two investigators independently reviewed all identified papers according to predefined eligibility criteria. These criteria included the following: (1) adult participants randomly allocated to groups; (2) patients with dyspepsia who fulfilled Rome $^9,10$ or Working Party $^{11}$ definitions; (3) negative findings at endoscopy (a diagnosis of hiatus hernia, $<$5 gastric erosions, or mild duodenitis was permitted); (4) evaluated intervention with a PPI; (5) used a comparison group that was either placebo, H$_2$-receptor antagonists, prokinetic therapy, antacids, or mucosal protecting agents (Helicobacter pylori eradication therapy was excluded); and (6) assessed symptoms of dyspepsia as an outcome. Trials that evaluated only patients with symptoms of gastroesophageal reflux disease, trials that evaluated only patients who were predominantly (>$20\%$) taking nonsteroidal anti-inflammatory drugs, and trials assessing outcomes at $<$1 week were excluded. A third reviewer was involved if there were any discrepancies, and a consensus view was taken.

The quality of trials was also evaluated according to specific criteria that have objectively been shown to influence trial results. $^{12}$ Quality scores were not used, because these have not been validated and may be unreliable. $^{13}$ The quality assessment focused on whether the methods used for randomization, concealment of allocation, and masking of participants and investigators were stated. Use of validated dyspepsia questionnaires was also noted. These factors were evaluated individually through meta-regression and subgroup analysis to assess whether any had an impact on the results of the meta-analysis.

**Data extraction.** A single investigator extracted data from eligible trials on a standardized form, and there was an unblinded check on the accuracy of the information by a second investigator. Data from intention-to-treat analyses were used whenever they were provided, and outcomes were recorded for the final visit. Dyspepsia outcomes were recorded in categories and were dichotomized a priori to improved/resolved versus same/worse dyspepsia symptoms. In practice, most eligible trials used an outcome of dyspepsia “cure,” which was defined as patients with no or minimal symptoms (symptoms not interfering with activities of daily living for 1 day per week).

**Data synthesis.** The effect of a particular therapy in each trial was expressed as a relative risk (RR), comparing the numbers remaining dyspeptic in the PPI group with those receiving an alternative therapy or placebo. If more than one dose of PPI was evaluated, the efficacy of increasing the dose in NUD was analyzed. If meta-analysis showed there was no difference between PPI doses, the data for different doses were pooled for each trial and compared with placebo or alternative therapy. RRs were pooled using a fixed-effect (Mantel–Haenszel) model, the appropriateness of which was assessed using a test of homogeneity. If significant heterogeneity ($P < .2$) existed between the studies, the relative risks were pooled using a random-effects model calculated according to the method of DerSimonian and Laird. $^{14}$ Reasons for heterogeneity in the results were explored, and the following factors were considered a priori: (1) proportion of patients with predominant reflux symptoms, (2) proportion of patients with $H. pylori$ infection, (3) method of randomization, (4) method of allocation of concealment, (5) method of blinding, (6) use of validated dyspepsia questionnaires, and (7) dosage, drug name, and duration of treatment. These factors were evaluated by subgroup analyses and meta-regression. Begg’s test $^{15}$ was used to assess publication bias, quality-related problems, or heterogeneity.

The outcome was expressed in terms of an RR of remaining dyspepsia. The number needed to treat was calculated using the mean dyspepsia rate in the placebo group (baseline rate [BR]) and the RR reduction (RRR) (RRR = 100(1 – RR)$\%$) according to the following formula:

$$NNT = \frac{100}{RRR \times BR}$$

All results were reported with 95% confidence intervals (CIs). Statistical analyses were undertaken in Stata (version 8.0; Stata Corp., College Station, TX) using the mean, metabs, and metaregress commands. The review was undertaken according to a protocol published in the Cochrane Library $^8$ and will be regularly updated as a Cochrane review as more information becomes available.

**Health Economic Analyses**

**Model structures and assumptions.** Estimates from the systematic review were incorporated into a Markov model (Data Pro release 10; TreeAge, Williamstown, MA) to establish the cost-effectiveness of PPI therapy in NUD. The patient group evaluated would all have had negative findings on endoscopy, and a gastroenterologist would have diagnosed NUD. US third-party payer, societal, and patient perspectives were taken. All models evaluated patients over a 1-year period and compared PPI with antacid therapy, which was assumed to act as an inexpensive placebo.

Patients entered the model with symptoms of dyspepsia and negative findings on endoscopy with a diagnosis of NUD made
by a gastroenterologist. A 30-day course of a PPI was administered. Nonresponders to PPI therapy were given reassurance, but no specific therapy was prescribed and no further investigations were performed over the duration of study (1 year). Three specialist visits were assumed to take place during the course of the year in nonresponders.16 In responders to PPI therapy, the drug was discontinued after 1 month. A proportion (20%) of patients remained well and required no further therapy,17 interventions, or office visits. The rest of the patients experienced a relapse and were placed on daily maintenance PPI therapy for the rest of the year, and 20% of these would have a relapse of symptoms. There are no long-term data for patients with NUD on maintenance therapy, so this assumption was based on patients with esophagitis on maintenance PPI therapy.18

Costs identified in the models. The US third-party payer perspective considered costs of medication and visits to the gastroenterologist as given in published sources.19 The cost of medication was varied between the over-the-counter price for a generic PPI and the price for a brand-name PPI.

The patient perspective assumed that patients would be asked to purchase PPI therapy or antacids over the counter. The travel cost of visiting a specialist by car was included in the model, as was time off work/loss of leisure time through dyspepsia symptoms. Both of these losses were conservatively valued at the US legal minimum wage and also at $25 per hour (Wisconsin’s minimum wage law; available at: http://www.dwd.state.wi.us/er/labor_standards_bureau/minimum_wage.htm. Accessed March 6, 2004). Data on loss of leisure time and time off work were obtained from a community survey of dyspepsia in 8473 subjects.20

The societal perspective included costs identified in both the patient and the third-party payer perspectives using over-the-counter PPI costs. The values assigned to all costs and outcomes used in these models are given in Table 1. Because a 1-year time frame was being evaluated, there was no discounting of costs or effects.

Analysis of economic data. There is statistical uncertainty in the costs and effects of alternative strategies of managing NUD. These have traditionally been evaluated by sensitivity analyses, but this approach assumes that all values in the range assessed are equally possible, which is not statistically correct. Sensitivity analyses can only assess the uncertainty in a few variables at a time, whereas an approach that incorporates all of the uncertainty in the model is preferable. Techniques have been developed that fulfill these criteria,21 and these were applied to the models evaluating PPI therapy in NUD. The main areas of uncertainty in the model are outlined in Table 1. The dispersion of the data is given by the 95% CIs, and a distribution is assigned to each of these variables. A β distribution was assigned to proportions, a log-normal distribution to RRs, and a γ distribution to cost data (Table 1). A second-order probabilistic analysis was then conducted using Monte Carlo simulation of 5000, and the results were expressed as cost-effectiveness acceptability curves. These plot the probability of a given strategy being cost-effective according to the maximum willingness to pay to have an extra month free from dyspepsia compared with the antacid strategy as baseline. Certain variables such as cost of drugs and value of time off work are not uncertain for a given patient but do vary in different settings. These variables were evaluated using sensitivity analyses.

## Results

### Systematic Review Data

**PPI therapy versus placebo.** A total of 11,796 citations were reviewed. Six eligible papers (reporting 8 trials)6-7,22-25 were identified that compared PPI therapy with placebo in 3293 patients (Table 2). (For reference 22, data from the authors and TAP Pharmaceutical Products US were provided to separate trials M96 and M97.) Four

<p>| Table 1. Assumptions Incorporated Into Markov Models Assessing Cost-effectiveness of PPI Therapy in NUD |</p>
<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>95% Confidence interval</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability will remain symptom-free at 1 month on antacid</td>
<td>77%</td>
<td>68%-84%</td>
<td>β</td>
</tr>
<tr>
<td>PPI efficacy at 1 month vs antacid</td>
<td>RR, 0.86</td>
<td>0.78–0.95</td>
<td>Log normal²</td>
</tr>
<tr>
<td>Probability will not need further therapy if symptom-free at 1 month</td>
<td>20%</td>
<td>13%-29%</td>
<td>β</td>
</tr>
<tr>
<td>Probability will remain symptom-free (if initially respond) after 1 year</td>
<td>80%</td>
<td>71%-87%</td>
<td>β</td>
</tr>
<tr>
<td>Cost of 1 month of PPI therapy</td>
<td>$19.99b</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Cost of 100 Gaviscon tablets</td>
<td>$8.59b</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Cost of visit to specialist</td>
<td>$232</td>
<td>0–30</td>
<td>NA</td>
</tr>
<tr>
<td>Mean mileage traveling to visit specialist</td>
<td>10</td>
<td>0–9</td>
<td>γ²⁰</td>
</tr>
<tr>
<td>Mean number of visits to specialist if still has dyspepsia</td>
<td>3</td>
<td>0–9</td>
<td>γ²⁰</td>
</tr>
<tr>
<td>Probability of taking time off work other than visiting a specialist</td>
<td>6%</td>
<td>5%-8%</td>
<td>β</td>
</tr>
<tr>
<td>Mean number of days off work</td>
<td>4</td>
<td>0–14</td>
<td>γ²⁰</td>
</tr>
<tr>
<td>Cost of travel per mile</td>
<td>$0.2</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Cost of time off work per hour</td>
<td>$5.15c</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA, not applicable.
²From systematic review.
ªPrice of 28 days of generic omeprazole and 100 tablets of Gaviscon. Available at: http://www.drugstore.com (accessed March 6, 2004).
In particular, the variation in results between studies was not associated with prevalence of *H. pylori* symptoms or gastroesophageal reflux symptoms. There was also no clear association with duration of treatment (2 weeks of therapy: RR, .83; 95% CI, .77–.89; 4 weeks of therapy: RR, .94; 95% CI, .77–1.15; 8 weeks of therapy: RR, .80; 95% CI, .73–.87). Meta-regression did not suggest that any of the pre-specified factors explained the heterogeneity between trials.

Impact of *H. pylori* status and dyspepsia subgroup on outcome. The variation in gastroesophageal reflux symptoms or *H. pylori* status may not explain the variation between trials, but these factors could still be im-

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blum et al</td>
<td>German multicenter RCT: double-blind, placebo-controlled trial</td>
<td>792 patients with normal EGD; Rome criteria for dyspepsia; 203 on placebo, 194 on ranitidine, 202 on omeprazole 10 mg, and 193 on omeprazole 20 mg</td>
<td>2 weeks ranitidine 150 mg od in the evening or omeprazole 10 mg od or 20 mg od in the morning vs placebo</td>
<td>1. Lack of dyspepsia symptoms requiring further management 2. Absence of global dyspepsia symptoms</td>
</tr>
<tr>
<td>Bolling-Sternevald et al</td>
<td>Scandinavian RCT: double-blind, placebo-controlled trial</td>
<td>197 patients with normal EGD; epigastric pain or discomfort; predominant reflux or IBS symptoms excluded</td>
<td>2 weeks omeprazole 20 mg od vs placebo</td>
<td>1. No epigastric pain on the last day of assessment 2. No dyspepsia symptoms on the last 2 days of assessment</td>
</tr>
<tr>
<td>Farup et al</td>
<td>Norwegian RCT: double-blind, placebo-controlled trial</td>
<td>24 patients with normal EGD; epigastric pain or discomfort; predominant reflux or IBS symptoms excluded</td>
<td>4 weeks omeprazole 20 mg od, 10 mg od, or placebo</td>
<td>Patients asked if had sufficient relief of dyspepsia symptoms (yes/no)</td>
</tr>
<tr>
<td>Peura et al (M96)</td>
<td>US RCT: double-blind RCT</td>
<td>393 evaluable patients with normal EGD and predominant upper abdominal pain</td>
<td>8 weeks lansoprazole 30 mg od, 15 mg od, or placebo</td>
<td>Complete relief of global dyspepsia symptoms</td>
</tr>
<tr>
<td>Peura et al (M97)</td>
<td>US RCT: double-blind RCT</td>
<td>382 evaluable patients with normal EGD and predominant upper abdominal pain</td>
<td>8 weeks lansoprazole 30 mg od, 15 mg od, or placebo</td>
<td>Complete relief of global dyspepsia symptoms</td>
</tr>
<tr>
<td>Talley et al (Bond)</td>
<td>Multinational RCTs: double-blind, placebo-controlled trial; 34% from primary care</td>
<td>642 patients with normal EGD and predominant epigastric pain/discomfort (a few reflux patients enrolled)</td>
<td>4 weeks omeprazole 20 mg od, 10 mg od, or placebo</td>
<td>Complete relief of epigastric pain/discomfort over last 3 days</td>
</tr>
<tr>
<td>Talley et al (Opera)</td>
<td>Multinational RCTs: double-blind, placebo-controlled trial; 8% from primary care</td>
<td>606 patients with normal EGD and predominant epigastric pain/discomfort (a few patients with reflux enrolled)</td>
<td>4 weeks omeprazole 20 mg od, 10 mg od, or placebo</td>
<td>Complete relief of epigastric pain/discomfort over last 3 days</td>
</tr>
<tr>
<td>Wong et al</td>
<td>Chinese RCT: double-blind, placebo-controlled trial</td>
<td>453 patients with normal EGD with predominant epigastric pain/discomfort</td>
<td>4 weeks lansoprazole 30 mg od, 15 mg od, or placebo</td>
<td>Validated dyspepsia questionnaire (Hong Kong Dyspepsia Index) assessed complete relief of symptoms</td>
</tr>
<tr>
<td>Wyeth trial, protocol 98/002</td>
<td>UK RCT: double-blind, placebo-controlled trial</td>
<td>151 patients with normal EGD and predominant epigastric pain/discomfort</td>
<td>8 weeks lansoprazole 30 mg od vs ranitidine 150 mg twice daily</td>
<td>Complete relief from epigastric pain over last 7 days</td>
</tr>
</tbody>
</table>

RCT, randomized controlled trial; EGD, esophagogastroduodenoscopy; od, once daily; IBS, irritable bowel syndrome.

papers (reporting 6 trials)\(^6,7,22,23\) provided evaluable data to compare low- and standard-dose PPI therapy in 2032 patients. There was no statistically significant difference between the 2 doses of PPI therapy (Figure 1) (RR of remaining dyspeptic on standard-dose PPI, .98; 95% CI, .92–1.04; \(P = .53\)) with no heterogeneity between trials (heterogeneity \(\chi^2 = 3.87, df = 5; P = .57\)). The results of the 2 doses of PPI therapy were therefore combined in these trials. PPI therapy was more effective than placebo, with 33% of the PPI group reporting no or minimal symptoms compared with 23% of the placebo group (RR of remaining dyspeptic, .86; 95% CI, .78–.95; \(P = .003\), random-effects model), resulting in a number needed to treat of 9 (95% CI, 5–25) (Figure 2). There was statistically significant heterogeneity between trials (heterogeneity \(\chi^2 = 30.05, df = 7; P < .001\) but no funnel plot asymmetry (Begg’s test; \(P = .54\)). Meta-regression did not suggest that any of the pre-specified factors explained the heterogeneity between trials.
important modifiers of the efficacy of PPIs in patients with NUD.

Five papers (reporting 7 trials) provided data on the impact of \textit{H pylori} status on efficacy of PPI therapy,\textsuperscript{6,7,22–24} and there was no difference in efficacy between infected and uninfected patients. There were 1219 \textit{H pylori}–positive patients, with 65% of the PPI group remaining dyspeptic compared with 74% of the placebo group (RR of remaining dyspeptic, .87; 95% CI, .81–.93). The efficacy of PPI therapy was almost identical in 2038 \textit{H pylori}–negative patients, with 65% of the treatment group remaining symptomatic compared with 74% of the control group (RR, .88; 95% CI, .78–.99).

Four papers (reporting 6 trials) provided data on the impact of the dyspepsia subgroup on the efficacy of PPI therapy,\textsuperscript{6,7,22,24} suggesting that treatment was more effective in patients with reflux symptoms. The classification of the reflux group varied between studies. Definitions included patients with predominant heartburn,\textsuperscript{6} patients who had symptoms of heartburn above a certain threshold,\textsuperscript{22} and patients with an abnormal 24-hour pH study (pH < 4 for >4% of the 24-hour recording).\textsuperscript{24}

Overall, there were 415 patients in the reflux group, with 55% of the PPI group remaining symptomatic compared with 74% of the placebo group (RR, .76; 95% CI, .66–.88; absolute risk reduction, 19%). There were 1394 patients with predominant epigastric pain, and 61% of the treatment group remained symptomatic compared with 72% of the placebo group (RR, .85; 95% CI, .7–.92; absolute risk reduction, 11%). A total of 683 patients had dysmotility-like dyspepsia, and 71% of the PPI group continued to have symptoms compared with 70% of the controls (RR, 1.02; 95% CI, 1.00–1.04; absolute risk reduction, −1%). There was therefore a trend for PPI therapy to be most effective in the reflux group and less effective in the epigastric pain group, with no statistically significant effect in the dysmotility group (Figure 3).

**Quality of the trials.** The quality of the trials was generally good, with 6 trials (4 papers)\textsuperscript{6,7,22,24} reporting adequate methods of randomization and use of a validated questionnaire to assess symptoms. Four trials (3 papers)\textsuperscript{6,7,23} reported adequate methods of blinding, and 3 trials (2 papers)\textsuperscript{6,7} reported adequate methods of concealment. There was no statistically significant effect of any of these quality criteria on the overall results using meta-regression, although the total number of trials is
In a subgroup analysis, there was a trend toward those reporting adequate concealment of allocation to show less of a treatment effect (RR, .94; 95% CI, .77–1.15) than those in which the method of concealment was not clear (RR, .82; 95% CI, .77–.86).

**PPI therapy versus H2-receptor antagonist therapy.** We identified 2 eligible trials (3 papers)8,23,26 (Table 2). One compared omeprazole 20 mg and 10 mg with ranitidine 150 mg over 2 weeks,23 and the other was a completed trial that is yet to be published (protocol 98/002; data on file, Wyeth Laboratories, Taplow, Maidenhead, England) evaluating lansoprazole 30 mg once daily versus ranitidine 150 mg twice daily over 8 weeks. The PPI strategy versus H2-receptor antagonist therapy was not statistically significant (P = .13). There was no significant heterogeneity between the 2 trials (heterogeneity χ² = .01; df = 1; P = .93).

**Health Economic Data**

PPI therapy for NUD is expensive from a health service perspective if the managed care price for PPIs is $90/month. The PPI strategy would cost on average an extra $326 for an extra 1.18 months free from dyspepsia, resulting in an incremental cost-effectiveness ratio of $278/month free from dyspepsia (Table 3). This figure does not incorporate the uncertainty in the data used in the model. When this is included in the model, a third-party payer could only be 95% certain that a PPI strategy for NUD would be cost-effective if they were willing to pay $517/month free from dyspepsia (Figure 5). This is much higher than the $180 patients are willing to pay for relief of reflux symptoms27 and is unlikely to be cost-effective. If over-the-counter prices are used, then a PPI strategy costs on average an extra $67 for an extra 1.18 months free from dyspepsia. This gives an incremental cost-effectiveness ratio of $57/month free from dyspepsia (Table 3). A third-party payer would be 95% certain that PPI therapy would be cost-effective provided

### Table 3. Cost-effectiveness of PPI Compared With Antacid Therapy in Patients With NUD

<table>
<thead>
<tr>
<th>Perspective</th>
<th>Strategy</th>
<th>Mean cost/patient</th>
<th>Marginal cost</th>
<th>Months free from dyspepsia/patient</th>
<th>Marginal effect</th>
<th>ICER ($/month free from dyspepsia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health service: PPI = $90</td>
<td>Antacid</td>
<td>$138.9</td>
<td>—</td>
<td>2.56</td>
<td>—</td>
<td>$277.51</td>
</tr>
<tr>
<td></td>
<td>PPI</td>
<td>$165.0</td>
<td>$326.10</td>
<td>3.73</td>
<td>1.18</td>
<td>—</td>
</tr>
<tr>
<td>Health service: PPI = $19.99</td>
<td>Antacid</td>
<td>$138.9</td>
<td>—</td>
<td>2.56</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>PPI</td>
<td>$205.9</td>
<td>$67.0</td>
<td>3.73</td>
<td>1.18</td>
<td>$56.98</td>
</tr>
<tr>
<td>Patient ($5.15/hour)</td>
<td>Antacid</td>
<td>$30.1</td>
<td>—</td>
<td>2.56</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>PPI</td>
<td>$80.6</td>
<td>$50.5</td>
<td>3.73</td>
<td>1.18</td>
<td>$42.94</td>
</tr>
<tr>
<td>Patient ($25/hour)</td>
<td>Antacid</td>
<td>$52.8</td>
<td>—</td>
<td>2.56</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>PPI</td>
<td>$105.8</td>
<td>$53.0</td>
<td>3.73</td>
<td>1.18</td>
<td>$45.11</td>
</tr>
<tr>
<td>Societal ($5.15/hour)</td>
<td>Antacid</td>
<td>$146.0</td>
<td>—</td>
<td>2.56</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>PPI</td>
<td>$212.3</td>
<td>$66.4</td>
<td>3.73</td>
<td>1.18</td>
<td>$56.47</td>
</tr>
<tr>
<td>Societal ($25/hour)</td>
<td>Antacid</td>
<td>$173.2</td>
<td>—</td>
<td>2.56</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>PPI</td>
<td>$237.2</td>
<td>$64.0</td>
<td>3.73</td>
<td>1.18</td>
<td>$54.49</td>
</tr>
</tbody>
</table>

ICER, incremental cost-effectiveness ratio.
they were willing to pay $94/month free from dyspepsia (Figure 5). The incremental cost-effectiveness ratios from a patient and societal perspective are even more favorable (Table 3 and Figure 5).

We also evaluated the cost-effectiveness of PPI therapy in different NUD subgroups, because the efficacy of therapy depended on which symptom predominated (Figure 3). PPI therapy remained cost-effective from a health care perspective (at $19.99/month of PPI therapy) in patients with predominant heartburn and epigastric pain (Table 4). The base case suggested that PPI therapy costs $45/month free from dyspepsia in patients labeled as having NUD with reflux symptoms. Incorporating all of the uncertainty in the data, we can be 95% certain that PPI therapy is cost-effective provided a third-party payer/patient is willing to pay $61/month free from dyspepsia. A similar result was seen with epigastric pain–predominant NUD, with a base case estimate of $55/month free from dyspepsia for PPI therapy (Table 4). There is no additional benefit of increasing the dose of PPI therapy.

Discussion

This is the first systematic review evaluating the efficacy of PPI therapy in NUD. We have shown that PPIs have a small but statistically significant effect on symptoms of NUD. This suggests that a modest proportion of patients with NUD have an acid-related disorder. There may be increased acid sensitivity in patients with NUD,28 because duodenal acidification has been shown to increase sensitivity to gastric distention.29 Studies have suggested, however, that peak and basal acid secretion in patients with NUD are similar to that in asymptomatic controls30,31 and symptoms are not reproduced by acid infusion at endoscopy.32 The evidence that acid has a direct effect on gastric mucosa to cause symptoms is therefore conflicting. Symptom relief in NUD may be related to changes in the volume of gastric secretion rather than to the magnitude of change in gastric pH. This is supported by this systematic review, because there is no additional benefit of increasing the dose of PPI therapy.

It is possible that the patients with NUD responding to PPI therapy are those with atypical endoscopy-negative gastroesophageal reflux disease.33 Case-control studies have suggested that the presence of nausea34 and bloating35 are predictors of poor outcome, whereas reflux symptoms are predictors of good therapeutic response to PPI therapy in patients with NUD.36 This is supported by the systematic review because patients with prominent reflux symptoms had the most benefit from PPI therapy, whereas active therapy was no better than placebo in those with “dysmotility” symptoms. It might be argued that the efficacy of PPI therapy in NUD is due to misclassification of patients with reflux disease. This is a possibility, but pragmatically this systematic review shows that some patients with normal findings on endoscopy and epigastric pain as the predominant symptom will benefit from PPI therapy. These are clinically useful data even if the PPI response is due to patients with atypical gastroesophageal reflux disease.

A mean placebo response rate of 23% in these trials is low compared with the 40% placebo response rate seen in trials of H2-receptor antagonists and prokinetic therapy in NUD.37 The placebo response rates were also relatively consistent between the PPI trials, varying from 16%33 to 31%.6 This is probably due to the use of complete relief of symptoms as a primary end point that the PPI trials adopted. Trials evaluating other pharmacologic therapies have usually used improvement in dyspepsia symptoms as an outcome,37 and this softer end

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### Table 4. Cost-effectiveness of PPI Compared With Antacid Therapy in NUD Symptom Subgroups From a Health Service Perspective

<table>
<thead>
<tr>
<th>NUD subgroup</th>
<th>Strategy</th>
<th>Mean cost/patient</th>
<th>Marginal cost</th>
<th>Months free from dyspepsia/patient</th>
<th>Marginal effect</th>
<th>ICER ($/month free from dyspepsia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reflux predominant</td>
<td>Antacid</td>
<td>$138.9</td>
<td>—</td>
<td>2.56</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>PPI</td>
<td>$230.1</td>
<td>$91.2</td>
<td>4.57</td>
<td>2.01</td>
<td>$45.41</td>
</tr>
<tr>
<td>Epigastric pain</td>
<td>Antacid</td>
<td>$138.9</td>
<td>—</td>
<td>2.56</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>PPI</td>
<td>$208.5</td>
<td>$69.6</td>
<td>3.82</td>
<td>1.27</td>
<td>$54.99</td>
</tr>
<tr>
<td>Dysmotility predominant</td>
<td>Antacid</td>
<td>$138.9</td>
<td>—</td>
<td>2.56</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>PPI</td>
<td>$166.4</td>
<td>$27.5</td>
<td>2.38</td>
<td>—18</td>
<td>Dominated</td>
</tr>
</tbody>
</table>

NOTE. PPI therapy cost $19.99.

ICER, incremental cost-effectiveness ratio.
point is likely to lead to higher placebo response rates. This hypothesis is supported by the mean placebo response rate of 29% in an updated systematic review of trials evaluating H pylori eradication therapies in NUD, which reported a mixture of symptom improvement and symptom cure as the primary end point. Indeed, 2 PPI trials also reported improvement in dyspepsia symptoms as a secondary outcome, and here the pooled placebo response rate was 51%. Similarly, the placebo response rate was 52% in the PPI trial that also reported “dyspepsia symptoms requiring no further management.”

These data suggest that using stringent criteria, such as complete absence of dyspepsia symptoms, reduces the placebo response rate, and this may be useful to adopt in future trials evaluating therapies in NUD.

Intragastric pH is greater in patients taking PPIs who are infected with H pylori. PPI therapy may therefore be more effective in H pylori–positive patients with NUD, as one study has suggested. Pooling all trial data suggests that symptom response is similar in H pylori–positive and –negative patients with NUD. H pylori status is unlikely to have a clinically important impact on efficacy of therapy in this patient group.

There is a statistically significant impact of PPI therapy in NUD, but it is uncertain whether this is clinically important. No therapy is particularly effective in NUD, with eradication of H pylori having a similarly modest effect on symptoms, and evidence for the efficacy of H2-receptor antagonists and prokinetic therapy is not robust. The question is therefore whether PPI therapy is cost-effective, especially because patients who respond are likely to need long-term treatment. Our economic model suggests that PPI therapy is not cost-effective from a health service perspective if the drug cost is $90/month. PPI therapy is now, however, available over the counter at $19.99 for 28 tablets. This reduction in price changes the results of the model, suggesting that PPI therapy is cost-effective in NUD even when incorporating all uncertainty in the data. The results using a societal perspective are similar. This is consistent with an increasing proportion of costs of dyspepsia relating to health service compared with 30–40 years ago. PPI therapy may be more cost-effective if reserved for patients with reflux or epigastric pain–predominant symptoms because PPI therapy is ineffective in dysmotility–predominant NUD.

This systematic review has the strength that it includes trials that are usually of good quality with a total sample size larger than any other intervention in NUD. The limitation of this study is that there are relatively few trials; therefore, factors that influence the results such as the quality of the trial and the length of therapy cannot be assessed with any power. The economic analysis uses current methods to incorporate the uncertainty in the data but does make assumptions on the long-term relapse rates on and off therapy that are based on extrapolations from patients with gastroesophageal reflux disease because there are little long-term data in NUD. The model is conservative because it assumes that patients with continued symptoms will have no further investigations. It is likely that a proportion of patients will undergo more tests if symptoms persist, and this would make PPI therapy even more cost-effective in NUD.

Over-the-counter PPI therapy may be used for both gastroesophageal reflux disease and NUD, because patients can find it difficult to distinguish between heartburn and epigastric pain. These data suggest that this approach is appropriate because PPI therapy is cost-effective at over-the-counter prices in NUD and in treating gastroesophageal reflux and peptic ulcer disease.

References


