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The Efficacy of Proton Pump Inhibitors in Adults with Functional Dyspepsia

Judy Y. Shiau, M.D., C.M., FRCPC
Vijay K. Shukla, B. Pharm., Ph.D.
Catherine Dubé, M.D., M.Sc., FRCPC

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1 The Ottawa Hospital, General Campus, Dept. of Internal Medicine, Ottawa, Ontario
2 Canadian Coordinating Office for Health Technology Assessment, Ottawa, Ontario
3 The Ottawa Hospital, Civic Campus, Dept of Internal Medicine, Division of Gastroenterology, Ottawa, Ontario
REVIEWERS

These individuals kindly provided comments on this report. CCOHTA takes sole responsibility for the final form and content.

CCOHTA Scientific Advisory Panel

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EXECUTIVE SUMMARY

Background: Functional dyspepsia refers to discomfort centred in the upper abdomen with no biochemical or organic cause (including at upper endoscopy). In Canada, the average primary care physician devotes 7% of clinical practice to patients with functional dyspepsia. Prior meta-analyses have demonstrated that prokinetic agents and H2-antagonists significantly reduce functional dyspepsia compared with placebo. To date, there is no comprehensive meta-analysis on the efficacy and safety of proton pump inhibitors (PPIs) in the treatment of functional dyspepsia. As the use of PPIs has increased in Canada by 228% from 1994 to 1998, a comparison of the effects of PPIs with other agents is needed.

Objectives:
Primary objective: To determine the efficacy of PPIs in the reduction of symptoms in adults with functional dyspepsia compared with placebo, prokinetic agents and H2-antagonists.

Secondary objectives:
- to determine if the effect of PPIs differs between symptom subgroups (dysmotility-like, or ulcer-like) in functional dyspepsia;
- to determine the safety of PPIs in functional dyspepsia; and
- to determine if the effect of PPIs differs in H.pylori positive patients with functional dyspepsia

Methods:
Design: Meta-analysis of randomized controlled trials (RCTs) that compared the efficacy of PPIs with placebo or H2-antagonists or prokinetic agents.

Subjects: Six studies comparing treatment with a PPI and placebo in a total of 2368 patients and one study comparing a PPI and H2-antagonist in 589 patients. No studies comparing a PPI with a prokinetic agent were identified.

Outcome: Number of patients experiencing either no symptoms (excellent control) or a significant improvement in symptoms (combined good and excellent control).

Results: PPIs were found to be more effective than placebo [odds ratio (OR) 1.81; 95% confidence interval (CI) 1.49-2.20 for excellent outcome and OR 1.53; 95% CI 1.29-1.81 for combined good and excellent response]. No significant heterogeneity was observed across the studies in both cases. Due to the small number of trials, sensitivity and subgroup analyses were limited. The role of H.pylori and PPIs in functional dyspepsia remains unclear. No significant difference was observed for excellent or for combined good and excellent outcomes between PPIs and H2-antagonists [OR 1.38; 95%CI 0.92 – 2.01 and OR 1.01; 95% CI 0.71 – 1.43, respectively]. PPIs had no significant side effects.
Discussion: PPIs are effective agents in reducing functional dyspepsia compared with placebo. For the combined good and excellent outcomes, an OR of 1.53 (95% CI 1.29-1.81) yields a number needed to treat (NNT) to improve one case of functional dyspepsia of 10; 95% CI 6.67-16.67. Cautious comparison with other meta-analyses of treatment agents used in functional dyspepsia can be made. Cisapride, a prokinetic agent, compared with placebo for combined good and excellent outcomes [OR 4.25; 95% CI 3.42-5.27], has a NNT of 3.12, 95% CI 2.7-3.57. H₂-antagonists are also effective compared with placebo for combined good and excellent outcomes [OR 2; 95% CI 1.16-3.45] with a NNT of 5.9; 95% CI 4.5-9.1.

Conclusion: This meta-analysis demonstrates that PPIs are effective in functional dyspepsia as compared with placebo. Based on other meta-analyses, prokinetic agents such as cisapride and H₂-antagonists have lower NNTs than PPIs and thus might appear more efficacious. Unfortunately, there are no direct comparison trials between the three agents and therefore there is no conclusive evidence that one agent is the best. Only one trial has demonstrated no difference between PPIs and H₂-antagonists. Further RCTs comparing PPIs, other prokinetic agents (such as domperidone), and H₂-antagonists, in *H.pylori* positive and negative patients with functional dyspepsia, are needed.
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1 INTRODUCTION

Dyspepsia, referring to pain or discomfort centred in the upper abdomen, is a common condition. In Canada, the prevalence of dyspepsia is 29%\(^1\) and the average primary care physician devotes 7% of clinical practice to patients with dyspepsia.\(^2\) An organic cause for dyspepsia is found in almost 40% of patients, the most common being gastroduodenal ulcer, gastroesophageal reflux disease, and gastric cancer. However, in more than 50% of patients no cause is apparent and the diagnosis is functional, or non-ulcer, dyspepsia.\(^3\) This meta-analysis focuses only on patients who have been investigated and diagnosed with functional dyspepsia. Therefore, results from this paper should not be applied to the treatment of uninvestigated dyspepsia.

Functional dyspepsia is defined as “12 weeks or more (within the last 12 months) of persistent or recurrent dyspepsia and no evidence of organic disease that is likely to explain the symptoms (including at upper endoscopy)” (Rome II consensus conference).\(^4\) Specifically, there should be no clinical, biochemical, endoscopic or ultrasonographic evidence of known organic disease to explain the symptoms. Studies included in this meta-analysis include patients who had no organic disease detected during upper endoscopy to explain their dyspepsia.

Within functional dyspepsia, three symptom groups were originally identified: ulcer-like dyspepsia, dysmotility-like dyspepsia, and reflux-like dyspepsia. Reflux-like dyspepsia was omitted by Rome II from the symptom subgroup because symptoms of heartburn or acid regurgitation have a high specificity for gastroesophageal reflux disease.\(^5\) The remaining two symptom subgroups, ulcer-like and dysmotility-like, are the more common symptoms associated with functional dyspepsia. Most studies on functional dyspepsia include a population with at least one or a combination of these two symptoms. An overlap of symptoms allowing reflux to be a minor component in the symptom complex but disallowing it as a predominant symptom is also found in studies on functional dyspepsia.\(^6\) The benefit in distinguishing between ulcer-like and dysmotility-like symptoms appears to be minimal because there is limited correlation between symptoms and pathophysiology.\(^3\) Whether therapy for functional dyspepsia can be tailored by symptom subgroup remains to be established.

Treatment options for functional dyspepsia include: antacids, eradication therapy for \(H. pylori\) positive patients, prokinetic agents, histamine \(H_2\)-antagonists, and proton pump inhibitors (PPIs). The first four therapeutic options have been evaluated as follows:

- Antacids have not been found to be better than placebo in one randomized controlled trial.\(^7\)
- Five separate reviews have evaluated eradication therapy of \(H. pylori\) in reducing symptoms of functional dyspepsia, and none have reached a definitive conclusion.\(^8\)-\(^12\)
- Both prokinetic agents and \(H_2\)-antagonists have been found to be more effective than placebo.\(^7,\,13\)
- A meta-analysis from the Cochrane Collaboration showed that PPIs have minimal efficacy in functional dyspepsia. However, this study was based on only three RCTs.\(^7\)
Therefore, the question remains as to whether PPIs are also effective in reducing symptoms in functional dyspepsia and how they compare with other agents such as H2-antagonists and prokinetic agents.

The importance of determining the efficacy of PPIs is particularly pertinent from the cost-effectiveness point of view. In Canada, there are currently three PPIs (lansoprazole, omeprazole, pantoprazole), four H2-antagonists (cimetidine, famotidine, nizatidine, ranitidine), and two motility agents (domperidone, metoclopramide) available. During the period 1995 to 1998, the utilization of PPIs for the treatment of dyspepsia in general increased 228%, while the use of H2-antagonists and prokinetic agents for the treatment of dyspepsia remained constant13 (Figure 1). Through this meta-analysis, we hope to clarify the role of PPIs in functional dyspepsia.
2 OBJECTIVES

Primary objective: To determine the efficacy of PPIs in the reduction of symptoms in adults with functional dyspepsia compared with placebo, prokinetic agents and H$_2$-antagonists.

Secondary objectives:
- To determine if the effect of PPIs differs between symptom subgroups (dysmotility-like, or ulcer-like) in functional dyspepsia;
- To determine the safety of PPIs in functional dyspepsia; and
- To determine if the effect of PPIs differs in *H. pylori* positive patients with functional dyspepsia.
3 METHODOLOGY

3.1 Literature Search

A comprehensive literature search was performed using Dialog® OneSearch® on MEDLINE®, HealthSTAR, EMBASE®, PASCAL, and SciSearch®. A Cochrane Controlled Trials Register search was also performed. The databases, keywords and search strategies for the OneSearch® are outlined in Appendix 1. There was no language restriction. The term “gastro-esophageal reflux” was included in the initial search strategy in order to minimize exclusion of any relevant articles. Articles that contained this term but also appeared to have a population of functional dyspeptic patients were retrieved as potentially relevant articles (n = 27). After careful reading of these articles, the articles consisting only of gastro-esophageal reflux patients or patients who did not have functional dyspepsia were excluded (n = 20), leaving seven remaining articles. The search was supplemented by manual searching of the reference lists from retrieved articles. Hand searches were also carried out for articles published since January 1995 in Gastroenterology and Gut. AstraZeneca, Solvay Pharma Inc., Byk Canada Inc., and Abbott Laboratories Ltd. were contacted for further identification of any unpublished materials.

3.2 Eligibility Criteria

Trials were eligible for inclusion only if the following criteria were met:

a. Study design: Randomized, controlled trials comparing PPIs with placebo, motility agents or H$_2$-antagonists.

b. Population:

Inclusion criteria: Adults (≥18 years old) who satisfy the diagnosis of functional dyspepsia (have no organic disease observed on endoscopy to explain the patient’s dyspepsia).

Exclusion criteria: Patients who have biliary tract or pancreatic disease, irritable bowel syndrome, peptic ulcer disease, cancer, gastroesophageal reflux disease, gastroparesis, lactose intolerance, malabsorption condition, parasitic infections, or who have been treated with eradication therapy for $H. pylori$.

c. Intervention: The administration of a PPI for at least one week.

d. Primary outcomes:

The primary outcome measure was the number of patients showing no symptoms (excellent) or mild symptoms (good) after the completion of treatment (global assessment scale). Within the trials, excellent symptom control was defined as “no symptoms”, "no symptoms last day on diary card", "complete absence of epigastric pain and discomfort", and “cure”. Good symptom control was described as “sufficient symptomatic relief”, “lack of dyspeptic symptoms requiring further management”, “overall treatment effect, better”, and “sufficient control of symptoms".
e. **Secondary outcome:**
The secondary outcome was a dyspeptic symptom score assessment, including:
- Individual dyspepsia symptom scores (epigastric pain/discomfort, post-prandial fullness, early satiety, anorexia, eructation, bloating, nausea, vomiting, belching);
- Adverse events.

### 3.3 The Selection Process

a. **Selection of potentially relevant studies:** One investigator (JS) reviewed citations and discarded irrelevant ones, based on the title and abstract of the publication. When an article’s relevance was uncertain, it was entered into the next phase of the study.

b. **Selection of relevant studies:** Originals or photocopies of the potentially relevant studies were independently assessed by two reviewers (JS, VS) in concordance with the set inclusion criteria. Disagreements were to be settled through a third party (CD).

c. **Assessment of study quality:** The quality of articles was assessed according to the validated three item Jadad scale. This scale assigns two points each for describing aspects of randomization and double blinding and one point for withdrawals and dropouts. The scale ranges from zero to five, with higher scores indicating more complete reporting. Concealment of each trial was also evaluated (Grade A= adequate, B= unclear C= inadequate). (Appendix 2).

### 3.4 Data Extraction

Two authors (JS, VS) extracted data independently on a data extraction form (Appendix 3). The completed forms were cross checked and any disagreements were resolved through consensus. From each trial, information regarding the trial design, patient characteristics (e.g. age, history of functional dyspepsia, history of alcohol or NSAID use), dosages, treatment period and outcomes were collected.

Data reporting on the primary outcome (number of patients showing no symptoms (excellent) or mild symptoms (good) of functional dyspepsia on a global assessment scale) were extracted and pooled to arrive at an overall estimate of the efficacy of PPIs and the comparator (active or placebo). For secondary outcomes, the number of patients free from individual symptoms of functional dyspepsia (epigastric pain/discomfort, post-prandial fullness, early satiety, anorexia, eructation, bloating, nausea, vomiting, belching), *H. pylori* status, and side effects were extracted and pooled to evaluate the efficacy and safety of PPIs and the comparator(s). Unsuccessful attempts were made to reach the authors of three abstracts for details about their trials.

### 3.5 Data Synthesis and Analysis

In one trial, the mean of two authors’ estimates from a bar graph containing pertinent data for both primary and secondary outcomes was used in the final analysis. In another trial, the number of patients with improved symptoms was estimated in both the intervention and control...
arms (60% in both arms) based on the trend seen in the other studies in the analysis and the fact that the study had shown a nonsignificant result. The exclusion of this trial in the sensitivity analysis did not significantly alter the final results.

Estimates of effectiveness of the intervention were expressed as odds ratios (OR) using the fixed effects model. If heterogeneity was detected, the random-effects model was used. The presence of publication bias was assessed by using the funnel plot of log odds ratio versus precision (1/SE) of individual studies included in the analysis. Sensitivity analysis was conducted on the influence of different factors on the outcomes, including: study quality, placebo run-in period, country of publication, and symptom subgroup. All calculations related to the meta-analysis were performed using the computer program Review Manager 4.1.
4 RESULTS

4.1 Selection and Quality Assessment of Studies

The complete search strategy yielded 886 unduplicated abstracts (880 from the Dialog<sup>®</sup> OneSearch<sup>®</sup>, four from the Cochrane Controlled Trials Register and two hand searched). Of these 886 abstracts, 27 potentially relevant studies were identified by a single reviewer. Of the 27 studies, two reviewers identified seven studies that completely satisfied the inclusion criteria<sup>14-20</sup>. There was 100% agreement between the two reviewers. All seven studies compared a PPI with a placebo in patients with functional dyspepsia. One of these studies also compared PPIs with placebo and an H<sub>2</sub>-antagonist<sup>14</sup>. Three studies were completed published trials<sup>14, 16, 19</sup> and the other four were abstracts<sup>15, 17, 18, 20</sup>. One of the abstracts<sup>17</sup> was the same trial as one of the published studies<sup>14</sup> and was excluded from the analysis, thus leaving six studies (n=6) for the final analysis.

The other twenty articles were excluded for the following reasons: patients had non-erosive gastro-esophageal reflux disease<sup>21-29</sup>, patients had gastro-esophageal reflux disease (GERD)<sup>30-33</sup>, no endoscopy was performed<sup>34, 35</sup>, the study was not an RCT<sup>36, 37</sup>, study was neither an RCT nor contained patients with functional dyspepsia<sup>38</sup>, and finally, no PPI was used<sup>39, 40</sup>. Quality assessment of these studies by the Jadad scale showed that one study was of high quality (quality score: 5), two were of moderate quality (quality scores: 3 and 4), and all three abstracts were low quality (quality scores: 0-2). Concealment was adequate for only one trial and unclear for the remaining five (Table 1). The two evaluators (JS, VS) were in complete agreement with the quality assessment.

4.2 Studies Comparing a PPI and Placebo

Six studies compared treatment with a PPI versus treatment with placebo for a total of 2368 patients. Five of the six studies were double-blinded, randomized, controlled trials of parallel design<sup>14, 16, 18-20</sup>. One trial<sup>15</sup> stated that it was double-blinded but did not specify randomization. Study quality was accounted for within the sensitivity analysis. Four studies disclosed information about support received from industry<sup>14, 16, 18, 19</sup>. Three studies were conducted in Scandinavia<sup>15, 16, 18</sup>, two in Germany<sup>14, 20</sup>, and one was conducted internationally<sup>19</sup> (Greece, UK, Canada, Scandinavia, Europe - including Germany). In two studies<sup>15, 18</sup> age eligibility was not mentioned, while the age criterion for patient entry in the remaining four studies was greater than 18 years.

In three studies, patients who had a history of at least one month of functional dyspepsia were recruited<sup>14, 16, 19</sup>. Two studies selected patients with symptoms for at least one week and one study did not provide any information about current and previous history of functional dyspepsia<sup>18, 20</sup>. Duration of the studies varied between two weeks<sup>14, 18, 20</sup> and four weeks<sup>15, 16, 19</sup>. All studies differed with respect to formal definitions of outcomes.

The use of non-steroidal anti-inflammatory drugs (NSAIDs) as a possible contributor to dyspeptic symptoms was considered as an exclusion criteria in only one study<sup>16</sup>. Two studies<sup>14, 19</sup> excluded patients with a history of alcohol abuse. Three studies had one-week run-in periods using occasional antacids for functional dyspepsia<sup>14, 16, 19</sup>. Run-in periods were not mentioned in the
three abstracts. Only two studies performed 24-hour esophageal pH monitoring to exclude randomization of GERD patients. Other studies attempted to minimize including patients with undocumented GERD by excluding patients who had a history of documented GERD on 24-hour pH monitoring or who had a history of heartburn.

### 4.3 Evaluation of Primary Outcomes in Studies Comparing a PPI and Placebo

Five out of the six studies provided information about the number of patients with global excellent or good outcomes. In the sixth study, this number was estimated by the authors.

A PPI was found to be more effective than placebo [OR: 1.81; 95% confidence interval (CI) 1.49 – 2.20] when assessing global excellent outcome only for patients showing no symptoms of functional dyspepsia (Figure 3a). Similarly, when looking at all six studies, the odds ratio in favor of PPI was 1.53 (95% CI 1.29 - 1.81) when combining good and excellent response (Figure 3b). No significant heterogeneity was observed with the studies used in these two outcome measures (chi-square 4.88, 6.56; df 3, 5; p=0.18, 0.26 respectively). The funnel plots obtained by plotting the log OR of primary outcomes versus precision of individual studies was symmetrical, at the combined outcome of good and excellent responses (Figure 4b). The funnel plot was asymmetrical when assessing global excellent outcome only, suggesting that a systematic bias exists among the studies (Figure 4a).

#### 4.3.1 Sensitivity Analysis

The influence of different factors on the outcomes was evaluated by carrying out multiple sensitivity analyses.

1. **Study quality**
   Data on the proportion of patients showing the combined good or excellent outcomes on the global assessment scale were analyzed separately for moderate-high and low quality studies. All the moderate-high studies were complete published articles while the low quality studies were abstracts. The OR of PPIs compared with placebo in the high and moderate studies was 1.43 (95% CI 1.18 - 1.73) and in the low quality studies was 1.94 (95% CI 1.36 - 2.78). Data were also collected for the combined good or excellent outcomes by removing the lowest quality trial in which the number of patients with improved symptom control had to be estimated. The OR after removing the lowest quality trial was 1.55 (95% CI 1.31 - 1.84). No significant heterogeneity was observed in any of these three subgroups (Table 2).

2. **Placebo run-in period**
   The three trials that had a placebo run-in period and defined functional dyspepsia as the presence of symptoms for at least one month were also the three articles that were published articles. Therefore, the sensitivity analysis of placebo run-in period yielded the same odds ratios as the sensitivity analysis based on study quality. The odds ratio for the trials without a run-in period was the same as that found for the three abstracts (Table 2).
3. **Country of publication**

For the three studies conducted in Scandinavian countries, the common OR for global excellent or good scores was 2.00 (95% CI 1.20 – 3.31). For the two studies conducted in Germany, the common OR for the same outcome was 1.55 (95% CI 1.17 – 2.04). The inclusion of the international study (which had recruitment sites in Scandinavia and in Germany) into either subgroup yielded odd ratios of 1.52 (95% CI 1.23 – 3.31) and 1.48 (95% CI 1.24 – 1.77) respectively. Heterogeneity across these subgroups was not significant (Table 2).

4.4 **Evaluation of Secondary Outcomes**

4.4.1 **Studies comparing PPIs and placebo between symptom subgroups**

Unfortunately, the data from the trials was insufficient to perform an analysis.

4.4.2 **Studies comparing PPIs and placebo in patients with functional dyspepsia who were positive for H.pylori**

Data on *H.pylori* patients could be drawn from four studies; *H.pylori* positive patients were diagnosed by 13C-urea breath tests, a combination of histology and rapid urease testing, and not mentioned in one study. In three studies, the subgroup of patients who were positive for *H.pylori* in the PPI and in the placebo arm were analysed. The OR for the combined global good or excellent scores was 1.61 (95% CI 1.23 – 2.10). As this result was significantly heterogeneous (p=0.05) (Table 3), the random effects model was used and the OR became 1.78 (95% CI 1.09 – 2.91). Within the group of patients on PPIs in four studies, patients positive for *H.pylori* were compared with patients who had responded to PPIs and those who had not. The OR for those who had responded, with combined global good or excellent scores, was 0.84 (95% CI 0.67 – 1.05) and for global excellent scores was 0.87 (95% CI 0.70-1.09). These subgroups were not significantly heterogeneous (Table 3).

4.4.3 **Studies comparing PPIs and H2-antagonists**

Only one trial compared the use of PPIs and H2-antagonists in the treatment of functional dyspepsia. In this trial, the OR for global good or excellent control was 1.01 (95% CI 0.71 – 1.43) and for excellent control was 1.38 (95% CI 0.92 – 2.01) (Table 4).

4.4.4 **Studies comparing PPI and placebo side effects**

Based on three studies which reported side effects, the OR for the use of PPIs compared with placebo was 0.97 (95% CI 0.68 – 1.39) (Table 3).
5 DISCUSSION

This discussion focuses on the results from the meta-analysis. First, the efficacy of PPIs compared with placebo is examined with respect to sources of clinical heterogeneity, sensitivity analyses, and subgroup analyses such as *H. pylori* status. Next we compare the results with a prior meta-analysis. Finally, the efficacy of PPIs is compared with other agents (prokinetic agents and H2-antagonists) in functional dyspepsia and the results are placed in a clinical context.

The use of PPIs is at least 50% more effective than placebo in reducing symptoms of functional dyspepsia (good-to-excellent outcomes) and at least 80% more effective than placebo in completely eliminating dyspeptic symptoms (excellent outcomes). According to one study,14 there is no statistically significant difference between PPIs and H2-antagonists in reducing functional dyspepsia. These results are based on the analysis of six double-blind, randomized controlled trials on adult patients with functional dyspepsia who received a PPI. All the trials have outcomes that are simplified within this meta-analysis to global excellent relief of dyspepsia or the combined global good-to-excellent relief of dyspepsia. As the funnel plot is symmetrical for the combined good-to-excellent relief of dyspepsia, the presence of publication bias is not significant. For excellent outcomes, the funnel plot is asymmetrical and therefore publication bias might be present. No statistically significant heterogeneity is observed within these six trials.

Although no statistical heterogeneity is observed, there are potential sources of clinical heterogeneity. The trials differ with respect to length of PPI use and dosage with only two of the six trials using the exact same regimen. The inclusion criteria vary from between one month of functional dyspepsia to one week of persistent symptoms. Only two studies formally exclude GERD with 24-hour pH monitoring in all enrolled patients. There is no validated outcome measure used for measuring symptom relief. NSAID use is excluded in only one trial and not documented in the others. Alcohol abuse is an exclusion criteria only in two studies while its use is recorded in another. Smoking is not significant in two studies.

Due to the small number of trials within this meta-analysis and the lack of data, it is not possible to perform subgroup analyses of the above. The sensitivity analyses based on study quality, placebo run-in period, and length of time of functional dyspepsia are based on the same grouping of studies and therefore are not helpful. The three studies of moderate to high quality are published articles that provide more detailed information. The three low quality studies are abstracts. Though the odds ratio for the low quality studies is 1.94 compared with 1.43 in the moderate-high quality studies, these two groups of studies are also the same groups for placebo run-in period and length of time of functional dyspepsia. Therefore, it is difficult to discern if any one or a combination of the three factors have an impact on the results. However, if the lowest quality study is removed from the sensitivity analysis, then the OR for low quality studies is reduced to 1.55, a value very similar to the base case. This pattern is consistent with the prior observation that the likelihood of demonstrating a large effect increases with poor study quality.41

The sensitivity analysis based on country of publication is also difficult to interpret because of overlap on quality of studies. Studies purely based in Scandinavian countries appear to be twice
as likely to reduce symptoms with the use of PPIs as compared with placebo. However these three studies are based on two low-quality trials and on one moderate quality trial of 24 patients. If the high quality international trial is added to the analysis, then the OR reduces down to the base case analysis.

Though the sensitivity analysis is limited, we can draw conclusions from the subgroup analyses of PPI side effects and *H. pylori* status. Due to the lack of symptom subgroup reporting in the six trials, we do not know if one subgroup (ulcer-like or dysmotility-like) benefits more or less by being treated with a PPI. In this meta-analysis, there is no difference in side effects between the use of PPIs and placebo. Based on three studies, patients who are *H. pylori* positive and treated with a PPI are 9% to 300% more likely to have a reduction in symptoms as compared to *H. pylori* positive patients treated with placebo. This wide effect range is due to the statistical heterogeneity of the studies, likely based on the above mentioned sources of clinical heterogeneity. When observing *H. pylori* positive patients who are treated with PPIs and comparing responders to non-responders, there is no significant difference in global excellent response or in the combined global good-to-excellent response. Therefore the benefit seen with PPIs when comparing *H. pylori* positive patients treated either with PPIs or placebo might be independent of *H. pylori* status, since little difference is seen between treating *H. pylori* negative or positive patients with PPIs. The relationship between PPIs and *H. pylori* status in functional dyspepsia needs to be clarified in further RCTs.

This study is more comprehensive than a meta-analysis published through the Cochrane Collaboration examining at the pharmacological interventions for functional dyspepsia. The Cochrane study, based on one published trial (the Bond and Opera study by Talley et al.), reported a relative risk reduction (RRR) of 12% (95% CI –1 to 24%) that was marginally, but not significantly, in favor of PPIs over placebo. The Cochrane RRR translates to an OR of 1.49 (95% CI 0.98 – 2.27) compared to our meta-analysis in which the OR is 1.53 (95% CI 1.29 - 1.81). Our study is based on three published trials, one of which is the Bond and Opera study, and three abstracts. Though we are unable to perform complete sensitivity and subgroup analyses due to unreported data, we have established that PPIs are significantly more effective than placebo in functional dyspepsia.

The results of this meta-analysis should be carefully compared with the results of meta-analyses on other therapeutic options for functional dyspepsia. For the combined good and excellent outcomes, the number needed to treat (NNT) to improve one case of functional dyspepsia with a PPI is 10 (95% CI 6.67-16.67). Other meta-analyses have shown that cisapride, a prokinetic agent, is also effective compared with placebo for combined good and excellent outcomes [OR 4.25 (95% CI 3.42-5.27)] with a NNT of 3.12 (95% CI 2.7 – 3.57). H2-antagonists compared with placebo have, for combined good and excellent outcomes, an OR of 2.0 (95% CI 1.16-3.45) with a NNT of 5.9 (95% CI 4.5-9.1). Based on the NNTs, we can hypothesize from these results that motility agents such as cisapride are more efficacious than H2-antagonists, which are in turn more efficacious than PPIs. However, these studies have not been designed to directly compare all three treatment options. Trials directly comparing these agents are needed but unfortunately lacking. In this meta-analysis, one trial comparing a PPI with an H2-antagonist yielded non-significant results. A meta-analysis of two studies demonstrated a non-significant benefit of prokinetic agents over H2-antagonists in functional dyspepsia [OR 2.38 (95% CI 0.81 – 7.14)].
Determining the best treatment agent for functional dyspepsia is further complicated by the fact that most RCT data on prokinetics are based on cisapride, a drug no longer available in Canada.

Our meta-analysis can only state with certainty that PPIs are effective in symptom control for patients with functional dyspepsia compared with placebo. The role of *H. pylori* remains unclear. Comparisons with prokinetic agents and H₂-antagonists should be made cautiously given the lack of valid RCTs directly comparing the three agents. If all three agents are at least equally efficacious, from a cost effectiveness perspective, physicians will have to think carefully when prescribing PPIs in functional dyspepsia. Physicians should also keep in mind that these results are limited to patients who have been investigated for dyspepsia and have no apparent organic reason for their symptoms. The results of this meta-analysis are likely more useful to subspecialists who encounter patients who have already had some type of work-up for their dyspepsia. For the primary care physician who is faced with patients with uninvestigated dyspepsia, these results are not generalizable to that population.
6 CONCLUSION

This meta-analysis demonstrates that PPIs reduce symptoms in functional dyspepsia compared with placebo and they also do not have significant side effects when compared with placebo. However, prokinetic agents and H₂-antagonists are also efficacious and have more favourable NNTs. Further RCTs comparing PPIs, other prokinetic agents such as domperidone, and H₂-antagonists, in *H. pylori* positive and negative patients with functional dyspepsia, are needed.
7 REFERENCES


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Figure 1: Canadian drug utilization data on H₂-antagonists, PPI and Cisapride
Potential relevant RCTs identified and screened for retrieval [n=27]

RCTs excluded [n=20]

Reasons:
(i) Non-erosive gastro-esophageal reflux disease = 9,
(ii) GERD = 4,
(iii) No endoscopy = 2,
(iv) Non-randomized trials = 2,
(v) Non-randomized trial and not functional dyspepsia = 1,
(vi) No PPI used = 2

RCTs retrieved for more detailed evaluation [n=7]

RCT excluded [n=1]

Reason: One abstract was the same trial as one of the published studies

RCTs included in the meta-analysis [n=6]
6 RCTs compared PPI with placebo, 1 RCT also compared PPI with H2-antagonist
Figure 3: Meta-Analysis Comparing Randomized Trials of PPI and Placebo in Patients with Functional Dyspepsia

Note: Results are based on number of patients with global excellent outcomes (3a) and combined global good and excellent response (3b).

Figure 3a

Comparison: 01 PPI vs placebo in symptom relief for functional dyspepsia
Outcome: 01 Excellent symptom control of all PPI vs placebo

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>OR (95% CI Fixed)</th>
<th>Weight %</th>
<th>OR (95% CI Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blum et al</td>
<td>129 / 355</td>
<td>31 / 203</td>
<td>17.8 [1.50, 3.84]</td>
<td>14.2</td>
<td>2.44 [1.26, 3.33]</td>
</tr>
<tr>
<td>Henges et al</td>
<td>81 / 131</td>
<td>61 / 138</td>
<td>8.0 [2.44, 26.56]</td>
<td>6.0</td>
<td>1.0 [1.17, 1.94]</td>
</tr>
<tr>
<td>Lauersen et al</td>
<td>37 / 87</td>
<td>14 / 190</td>
<td></td>
<td>52.1</td>
<td></td>
</tr>
<tr>
<td>Taley et al</td>
<td>307 / 826</td>
<td>119 / 422</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total(95%CI)</td>
<td>557 / 1439</td>
<td>225 / 853</td>
<td></td>
<td>100.0</td>
<td>1.0 [1.46, 2.29]</td>
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</table>

Test for heterogeneity chi-square=4.88, df=3, p=0.18
Test for overall effect z=5.04, p<0.00001

Favours control Favours treatment

Figure 3b

Comparison: 02 PPI vs Placebo in symptom relief for functional dyspepsia
Outcome: 01 Good and excellent symptom control for all doses of PPI vs placebo

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>OR (95% CI Fixed)</th>
<th>Weight %</th>
<th>OR (95% CI Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blum et al</td>
<td>237 / 385</td>
<td>107 / 203</td>
<td>26.3 [1.86, 1.89]</td>
<td>5.33 [0.92, 1.54]</td>
<td>2.44 [1.26, 3.33]</td>
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<tr>
<td>Farup et al</td>
<td>9 / 114</td>
<td>2 / 10</td>
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<td>0.5</td>
<td>5.33 [0.92, 1.54]</td>
</tr>
<tr>
<td>Henges et al</td>
<td>81 / 131</td>
<td>61 / 138</td>
<td>10.8 [2.04, 6.3]</td>
<td>4.1</td>
<td>1.0 [1.17, 1.94]</td>
</tr>
<tr>
<td>Knutsson et al</td>
<td>22 / 30</td>
<td>23 / 36</td>
<td></td>
<td>5.4</td>
<td>1.0 [1.17, 1.94]</td>
</tr>
<tr>
<td>Lauersen et al</td>
<td>43 / 79</td>
<td>25 / 76</td>
<td></td>
<td>53.2</td>
<td>1.0 [1.17, 1.94]</td>
</tr>
<tr>
<td>Taley et al</td>
<td>496 / 925</td>
<td>215 / 422</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total(95%CI)</td>
<td>507 / 1461</td>
<td>434 / 857</td>
<td></td>
<td>100.0</td>
<td>1.5 [1.23, 1.81]</td>
</tr>
</tbody>
</table>

Test for heterogeneity chi-square=6.55, df=5, p=0.26
Test for overall effect z=4.92, p<0.00001

Favours treatment Favours control
**Figure 4:** Funnel Plot of Studies where the Number of Patients with Global Excellent (4a) and Combined Global Good and Excellent Outcomes (4b) were used to Calculate OR.

Figure 4a

![Funnel Plot 4a](image)

Figure 4b

![Funnel Plot 4b](image)
Table 1: List of randomized controlled trials comparing PPIs and placebo

<table>
<thead>
<tr>
<th>Study</th>
<th>Jadad scale quality</th>
<th>Concealment</th>
<th>Design &amp; Duration</th>
<th>Drug Dose</th>
<th>Patients randomized</th>
<th>Global evaluation (number of patients)</th>
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<tr>
<td></td>
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<td></td>
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<td>PPI</td>
<td>Plb</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Exc/total</td>
<td>Exc or good/total</td>
</tr>
<tr>
<td>Talley NJ et al. 1998</td>
<td>5</td>
<td>Adequate</td>
<td>DB/PL 4 wks</td>
<td>Ompz 20 or 10mg od</td>
<td>836</td>
<td>426</td>
</tr>
<tr>
<td>Blum AL et al. 2000</td>
<td>4</td>
<td>Undear</td>
<td>DB/PL 2 wks</td>
<td>Ompz 20 or 10mg od</td>
<td>395</td>
<td>203</td>
</tr>
<tr>
<td>Farup PG et al. 1999</td>
<td>3</td>
<td>Undear</td>
<td>DB/PL 4 wks</td>
<td>Ompz 20 or 10mg od</td>
<td>14</td>
<td>10</td>
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<td>Hengels KJ et al. 1998</td>
<td>2</td>
<td>Undear</td>
<td>DB/PL 2 wks</td>
<td>Lan 15mg od</td>
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<td>138</td>
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<tr>
<td>Luntsen K et al. 1996</td>
<td>2</td>
<td>Undear</td>
<td>DB/PL 2 wks</td>
<td>Ompz 20mg bid</td>
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<td>97</td>
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<tr>
<td>Knuhtsen S et al. 1994</td>
<td>1</td>
<td>Undear</td>
<td>DB/PL 4 wks</td>
<td>Ompz 40mg od</td>
<td>36</td>
<td>38</td>
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</table>

PPIs: proton pump inhibitors, Plb: placebo, Exc: excellent, DB/PL: double-blind/parallel, Ompz: Omeprazole, Lan: Lansoprazole, od: once a day, bid: twice a day, NA: not available

Table 2: Sensitivity Analyses

<table>
<thead>
<tr>
<th>Item</th>
<th>Excellent or Good Outcome</th>
<th>OR (95% CI)</th>
<th>Test of heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Q statistics (df)</td>
<td>p value</td>
</tr>
<tr>
<td>Base case</td>
<td>14-16, 18-20</td>
<td>1.53 (1.29-1.81)</td>
<td>6.56 (5)</td>
</tr>
<tr>
<td>Study quality</td>
<td>14, 16, 19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-moderate</td>
<td>15, 18, 20</td>
<td>1.43 (1.18-1.73)</td>
<td>2.01 (2)</td>
</tr>
<tr>
<td>Low</td>
<td></td>
<td>1.94 (1.36-2.78)</td>
<td>2.31 (2)</td>
</tr>
<tr>
<td>Placebo run-in period</td>
<td>14, 16, 19</td>
<td>1.43 (1.18-1.73)</td>
<td>2.01 (2)</td>
</tr>
<tr>
<td>Present</td>
<td>15, 18, 20</td>
<td>1.94 (1.36-2.78)</td>
<td>2.31 (2)</td>
</tr>
<tr>
<td>Country of publication</td>
<td>15, 16, 18</td>
<td></td>
<td></td>
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<tr>
<td>Scandinavia only</td>
<td>14, 20</td>
<td>2.00 (1.20-3.31)</td>
<td>3.37 (2)</td>
</tr>
<tr>
<td>Germany only</td>
<td>15, 16, 18, 19</td>
<td>1.55 (1.17-2.04)</td>
<td>1.90 (1)</td>
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<tr>
<td>Scandinavia + Intl</td>
<td>14, 19, 20</td>
<td>1.52 (1.23-1.88)</td>
<td>4.65 (3)</td>
</tr>
<tr>
<td>Germany + Intl</td>
<td></td>
<td>1.48 (1.24-1.77)</td>
<td>2.06 (2)</td>
</tr>
</tbody>
</table>

OR: odds ratio, CI: confidence interval, df: degrees of freedom, Intl: International
### Table 3: Subgroup Analyses

<table>
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<tr>
<th>Item</th>
<th></th>
<th>Excellent or Good Outcome</th>
<th>Test of heterogeneity</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>OR (95% CI)</td>
<td>Q statistics (df)</td>
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<tr>
<td>Comparison of PPI vs plb in <em>H. pylori</em> positive pts</td>
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<td>1.61 (1.23-2.10)</td>
<td>6.01 (2)</td>
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<tr>
<td></td>
<td>14, 18, 20</td>
<td>Fixed effects</td>
<td>Random effects</td>
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<tr>
<td></td>
<td></td>
<td>1.78 (1.09-2.91)</td>
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<tr>
<td>Comparison of <em>H. pylori</em> status in pts who responded to a PPI</td>
<td></td>
<td>0.84 (0.67-1.05)</td>
<td>3.78 (3)</td>
</tr>
<tr>
<td></td>
<td>14, 16, 18, 20</td>
<td></td>
<td></td>
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<tr>
<td>Comparison of PPI and plb side effects</td>
<td></td>
<td>0.97 (0.68-1.39)</td>
<td>4.14 (2)</td>
</tr>
<tr>
<td></td>
<td>14, 18, 20</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**OR:** odds ratio, **CI:** confidence interval, **df:** degrees of freedom, **plb:** placebo, **pts:** patients

### Table 4: Randomized Controlled Trial Comparing PPI and H₂ Antagonist

<table>
<thead>
<tr>
<th>Study</th>
<th>Jadad scale quality</th>
<th>Concealment</th>
<th>Design &amp; Duration</th>
<th>Drug Dose</th>
<th>Patients randomized</th>
<th>Global evaluation (number of patients)</th>
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<td>PPI</td>
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<td>Blum AL et al. 2000</td>
<td>4</td>
<td>unclear</td>
<td>DB/PL 2 wks</td>
<td>Ompz: 20 or 10mg od</td>
<td>Ran 150mg qhs</td>
<td>395</td>
</tr>
</tbody>
</table>

**PPI:** proton pump inhibitor, **H₂:** H₂ antagonist, **Ran:** Ranitidine, **Exc:** excellent, **DB/PL:** double-blind/parallel, **Ompz:** Omeprazole, **od:** once a day, **qhs:** each night
## Appendix 1: Dialog® Onesearch® Strategy

<table>
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<th>KEYWORDS</th>
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<td>Dialog OneSearch®</td>
<td>1966+</td>
<td>1. (esophagitis, peptic OR gastroparesis OR gastric emptying OR hiatal)/de</td>
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<td></td>
<td>1975+</td>
<td>2. (dyspepsia/de NOT peptic ulcer/de) OR nonulcer(w)dysepsis? OR functional(w)dysepsis? OR ulcer(w)like(w)dysepsis? OR essential(w)dysepsis?/ti,ab OR gastroosophageal reflux/de OR ([gastro esophageal(w)reflux? OR gastro?esophag?(w)reflux? OR gerd? OR gerd]/ti,ab OR esophagitis, peptic/de OR [peptic(w)esophagitis] OR peptic(w)oesophagitis OR reflux(w)esophagitis OR reflux(w)oesophagitis]/ti,ab OR heartburn/de OR (heartburn OR eructation]/ti,ab OR (eructation OR flatulence)/de OR flatulence/ti,ab OR /flat OR gastropares? OR stomach(w)paresis OR belch? OR acid(w)reflux? OR bloat? OR burp? OR early(w)satiety OR hiat?(w)hernia? OR gastric(w)acid(w)secretion? OR stomach(w)acid(w)secretion? OR gastritic? OR gastritis(w)erosion? OR stomach(w)erosion?]/ti,ab</td>
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<tr>
<td>MEDLINE® (File 155)</td>
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<td>3. proton pump(iai)</td>
</tr>
<tr>
<td>HealthSTAR (File 151)</td>
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<td>4. proton(w)pump(w)inhibitor?/ti,ab OR omeprazole/de OR (omeprazole OR lansoprazole OR pantoprazole OR timiprazol)/de OR nizaprazol? OR prevacid OR protonix OR prevpac OR prilosec OR aciphex OR losec OR pantoloc/ti,ab OR (73590-58-6 OR 103577-45-3 OR 102625-70-7 OR 117976-89-3)</td>
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<td></td>
<td></td>
<td>5. dt=(clinical trial OR clinical trial, phase i OR clinical trial, phase ii OR clinical trial, phase iii OR clinical trial, phase iv OR meta-analysis OR controlled clinical trial OR randomised controlled trial OR multicenter study)</td>
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<tr>
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<td>6. clinical trials! OR (comparative study OR double-blind method OR random allocation OR placebo)/de</td>
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<td>7. [random? OR rct? OR placebo? OR controlled(w)trial? OR controlled(w)clinical(w)trial? OR double(w)blind OR meta-analysis OR meta(w)analy? OR research(w)integration OR research(w)overview? OR quantitative(w)review? OR quantitative(w)overview? OR research(w)overview? OR methodologic(w)review? OR</td>
</tr>
<tr>
<td>DATABASES</td>
<td>LIMITS</td>
<td>KEYWORDS</td>
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<tr>
<td>EMBASE® (File 73)</td>
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<td>methodologic(w)overview? OR systematic(w)overview? OR systematic(w)review? OR integrative(w)research OR quantitative(w)synthesis? OR comparative(w)study?</td>
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<td>PASCAL (File 144)</td>
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<td>comparative study OR randomized controlled trial OR prospective study OR retrospective study OR meta analysis OR clinical trial OR multicenter study OR phase 1 clinical trial OR phase 2 clinical trial OR phase 3 clinical trial OR phase 4 clinical trial OR randomization OR controlled study/or randomized OR controlled study OR placebo OR randomized controlled trial OR clinical trial OR phase 1 OR phase 2 OR phase 3 OR phase 4</td>
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<td>(S2 OR S11) AND (S4 OR S12) AND (S7 OR S13)</td>
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## Appendix 2: Rating Scale Used to Assess Quality of Studies

### Quality Assessment of RCTs:

<table>
<thead>
<tr>
<th>Jadad Scale</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Was the study described as randomized?</td>
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<tr>
<td>Was the method of randomization described?</td>
<td></td>
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<tr>
<td>If the method of randomization was explained was it appropriate?</td>
<td></td>
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<tr>
<td>Randomization score:</td>
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<tr>
<td>2. Was the study described as double blind?</td>
<td></td>
</tr>
<tr>
<td>Was the method of double blinding described?</td>
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<tr>
<td>If the method of blinding was explained was it appropriate?</td>
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<tr>
<td>Double blind score:</td>
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</tr>
<tr>
<td>3. Was there a description of withdrawals and dropouts?</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>/5</td>
</tr>
</tbody>
</table>

### Scoring of the Jadad Scale:

Either give a score of 1 point for each ‘yes’ and 0 points for each ‘no’. There are no in-between marks.

Give 1 additional point if: For question 1, the method to generate the sequence of randomization was described and it was **appropriate** (table of random numbers, computer generated, coin tossing etc.)

and / or

If on question 2 the method of double-blinding was described and it was **appropriate** (identical placebo, active placebo, dummy, etc.)

Deduct 1 point if: For question 1, the method to generate the sequence of randomization was described and it was **inappropriate** (patients were allocated alternately, or according to date of birth, hospital number, etc.)

and / or

For question 2, the study was described as double-blind but the method of blinding was **inappropriate** (e.g. comparison of tablet vs. injection with no double dummy).

### Other Quality assessment item

Was the adequacy of allocation concealment described? Adequate / inadequate / unclear
**Appendix 3: Data Extraction Form**

<table>
<thead>
<tr>
<th>EFFICACY STUDY RESULTS</th>
<th>REVIEWERS INITIALS________</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study no:</td>
<td>Industry sponsorship: yes/no/no info :</td>
</tr>
</tbody>
</table>

**REFERENCE:**

**METHODS:**

<table>
<thead>
<tr>
<th>IS THIS STUDY DOUBLE BLINDED:</th>
<th>YES / NO Parallel/Cross-over</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>STUDY ARM</th>
<th>DOSE AND FREQUENCY</th>
<th>DURATION OF TREATMENT</th>
<th>PLACEBO RUN IN PERIOD BEFORE RDMZ</th>
</tr>
</thead>
</table>

**TARGET SYMPTOMS :**

- Epigastric/Abdominal Pain/Discomfort: ( )
- Bloating/Abdominal Distention: ( )
- Nausea and/or Vomiting: ( )
- Belching: ( )
- Early Satiety/Full Feeling: ( )
- Heart Burn: ( )
- Acid Regurgitation: ( )
- Other Symptoms: ( )

**SCALE USED FOR SEVERITY OF SYMPTOMS ASSESSMENT:**

(a) Categorical Scale: e.g. NO SYMPTOMS, MILD SYMPTOMS, MODERATE SYMPTOMS AND SEVERE SYMPTOMS

- 4-Point Scale: ( )
- 5-Point Scale: ( )
- 6-Point Scale: ( )
- 7-Point Scale: ( )

(b) Visual Analog Scale (VAS):

**SCALE USED FOR THE FREQUENCY OF THE SYMPTOMS:**

**GLOBAL ASSESSMENT :**

- Poor: No Change or Deterioration of Symptoms ( )
- Fair: Clear but Limited Improvement ( )
- Good: Considerable Overall Improvement ( )
- Excellent: Complete or Almost Complete Disappearance of Symptoms ( )
### RESULTS: PATIENT CHARACTERISTICS

<table>
<thead>
<tr>
<th>NUMBER OF PATIENTS</th>
<th>SCREENED</th>
<th>ELIGIBLE</th>
<th>RANDOMIZED</th>
<th>EVALUABLE</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>SEX</th>
<th>M / F</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>MEAN AGE (YEARS)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>DYSPEPSIA HISTORY</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>PRESENT EPISODES</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>SMOKERS</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>ALCOHOL</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>BASELINE INTENSITY OF DYSPEPSIA</th>
</tr>
</thead>
</table>

### RESULT: SYMPTOMS RESOLUTION

<table>
<thead>
<tr>
<th>IMPROVEMENT IN DYSPEPSIA SYMPTOM SCORES (ALL RATED ON 4-POINT SCALE)</th>
<th>EPIGASTRIC PAIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLOATING</td>
<td></td>
</tr>
<tr>
<td>NAUSEA</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OR</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>NUMBER OF PATIENTS BECOME SYMPTOM FREE</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>EARLY SATIETY</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>BELCHING</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>HEART BURN</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>OVERALL SCORES</th>
</tr>
</thead>
</table>

### GLOBAL ASSESSMENT SCALE

<table>
<thead>
<tr>
<th>PATIENTS WITHOUT SYMPTOMS</th>
<th>(EXCELLENT)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>WITH SIGNIFICANT IMPROVEMENT IN SYMPTOMS</th>
<th>(GOOD)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>TOTAL</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>DYSPEPSIA - SYMPTOM FREE DAYS</th>
</tr>
</thead>
</table>

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Appendix 4: List of Excluded Studies (n=20)

a) Patients with non-erosive gastro-esophageal reflux disease (n=9)


b) Patients with gastro-esophageal reflux disease (GERD)


Bate CM, Green JR, Axon AT, Murray FE, Tildesley G, Emmas CE, et al. Omeprazole is more effective than cimetidine for the relief of all grades of gastro-oesophageal reflux


c) No endoscopy was performed (n=4)


Meineche-Schmidt V, Christensen E. Which dyspepsia patients will benefit from omeprazole treatment? Analysis of a Danish multicenter trial. *Am J Gastroenterol* 2000;95:2777-83.

d) Not a RCT (n=2)


e) Study was neither a RCT nor had patients with functional dyspepsia (n=1)


f) No proton PPI used (n=2)
