



lasting at least 1 month. This can be associated with any other upper gastrointestinal symptom such as epigastric fullness, nausea, vomiting, or heartburn, provided epigastric pain is the patient's primary concern. Although this definition may differ slightly from those used in specific trials, we feel it best represents the clinical problem and the breadth of trial definitions used across time, location, and patient populations. Functional dyspepsia refers to patients with dyspepsia where endoscopy (and other tests where relevant) has ruled out organic pathology that explains the patient's symptoms.

This guideline will focus on initial investigations for dyspepsia such as *Helicobacter pylori* (*H. pylori*) testing and endoscopy as well as pharmacological therapies such as *H. pylori* treatment, PPIs, and prokinetic therapy. We do not address the management of organic pathology that may present with dyspepsia identified at endoscopy, such as esophagitis or peptic ulcer disease as there are other ACG guidelines for these specific diseases (17). Further, when *H. pylori* testing or treatment is recommended we do not specify which investigation or which therapy to use, as this will be addressed in an ACG guideline on *H. pylori* and other recent guidelines have been published (18). The treatment sections warrant an important caveat. Recommendations are made based on available data for patients who fail initial standard therapy such as *H. pylori* eradication, PPI therapy, and use of a TCA or prokinetic agent. These recommendations are made in a sequential manner recognizing that, with each therapeutic trial, there is significant time and expense involved in treating these patients, and that there is little data available prospectively evaluating dyspeptic patients who fail consecutive therapies. However, since this disorder is common, and since patients do not uniformly respond to one medication, we believe it important to address key clinical treatment options, despite limited data. The assumption of this latter point is that patients that continue to consult due to persistent symptoms desire further treatment.

The global literature was reviewed and this guideline takes an international perspective. Nevertheless, the main viewpoint taken related to the US and Canada and our recommendations may not apply to other countries in some instances. We have indicated in the text specific areas where local variations in incidence of disease or availability of medication may result in different approaches being recommended in other countries.

All recommendations are listed in **Table 1**.

## GUIDELINE METHODOLOGY

The group was chosen to represent a US and Canadian secondary and tertiary care perspective on managing dyspepsia with experience in guideline methodology, motility, endoscopy, and pharmacological therapies. The group formulated statements that followed the PICO (population, intervention, comparator, outcome) format to guide the search for evidence (**Table 2**). Systematic reviews were conducted for initial management strategies of uninvestigated dyspepsia as well as for pharmacological therapies for FD that supported the PICO statements. An experienced professional developed the search strategies for MEDLINE, EMBASE

**Table 1. Summary and strength of recommendations**

1. We suggest dyspepsia patients aged 60 or over have an endoscopy to exclude upper gastrointestinal neoplasia. Conditional recommendation, very low quality evidence.
2. We do not suggest endoscopy to investigate alarm features for dyspepsia patients under the age of 60 to exclude upper GI neoplasia. Conditional recommendation, moderate quality evidence.
3. We recommend dyspepsia patients under the age of 60 should have a non-invasive test for <i>H. pylori</i> , and therapy for <i>H. pylori</i> infection if positive. Strong recommendation, high quality evidence.
4. We recommend dyspepsia patients under the age of 60 should have empirical PPI therapy if they are <i>H. pylori</i> -negative or who remain symptomatic after <i>H. pylori</i> eradication therapy. Strong recommendation, high quality evidence.
5. We suggest dyspepsia patients under the age of 60 not responding to PPI or <i>H. pylori</i> eradication therapy should be offered prokinetic therapy. Conditional recommendation very low quality evidence.
6. We suggest dyspepsia patients under the age of 60 not responding to PPI or <i>H. pylori</i> eradication therapy should be offered TCA therapy. Conditional recommendation low quality evidence.
7. We recommend FD patients that are <i>H. pylori</i> positive should be prescribed therapy to treat the infection. Strong recommendation, high quality evidence.
8. We recommend FD patients who are <i>H. pylori</i> -negative or who remain symptomatic despite eradication of the infection should be treated with PPI therapy. Strong recommendation, moderate quality evidence.
9. We recommend FD patients not responding to PPI or <i>H. pylori</i> eradication therapy (if appropriate) should be offered TCA therapy. Conditional recommendation, moderate quality evidence.
10. We suggest FD patients not responding to PPI, <i>H. pylori</i> eradication therapy or tricyclic antidepressant therapy should be offered prokinetic therapy. Conditional recommendation, very low quality evidence.
11. We suggest FD patients not responding to drug therapy should be offered psychological therapies. Conditional recommendation, very low quality evidence.
12. We do not recommend the routine use of complementary and alternative medicines for FD. Conditional Recommendation, very low quality evidence.
13. We recommend against routine motility studies for patients with FD. Conditional recommendation, very low quality evidence.
14. We suggest motility studies for selected patients with FD where gastroparesis is strongly suspected. Conditional recommendation, very low quality evidence.
FD, functional dyspepsia; <i>H. pylori</i> , <i>Helicobacter pylori</i> ; PPI, proton pump inhibitor; TCA, tricyclic antidepressant.

and the Cochrane Controlled Trials Register and these databases were searched from inception to December 2015 (**Appendix 1**). Two independent researchers (PMM and Cathy Yuan) assessed eligibility and extracted data. We took the most stringent definition of dyspepsia improvement as the outcome if more than one definition of improvement was given (i.e., the definition that resulted in the lowest placebo response rate). Summary statistics were expressed as relative risk (RR) and number needed to treat (NNT) with 95% confidence intervals (CI) and a random effects model was used. We used the GRADE approach (19) to assess the quality of evidence and give strength of recommendation.

**Table 2.** PICO statements evaluated in the dyspepsia guideline

Informal Question	PICO Question				Method
	Population	Intervention(s)	Comparator	Outcome	
What is the most appropriate initial evaluation for patients ≥60 years of age with dyspepsia?	Adult uninvestigated dyspepsia patients stratified by age	Endoscopy	Symptomatic management	1. Upper GI cancers detected 2. Early upper GI cancers detected 3. Rates of upper GI malignancy by age 4. Adverse events	Observational data
Are alarm features useful in identifying dyspepsia patients with upper GI malignancy?	Adult uninvestigated dyspepsia patients	Patients with one or more alarm features	Patients with no alarm features	Sensitivity, specificity, positive and negative likelihood ratios for identifying upper GI malignancy and all organic pathology	Observational data (cross-sectional, case-control and cohort studies)
Is <i>H. pylori</i> test and treat the most appropriate initial strategy for patients <60 years of age with dyspepsia?	Adult uninvestigated dyspepsia patients	<i>H. pylori</i> test and treat	1. Endoscopy 2. Empirical PPI therapy	1. Dyspepsia resolution 2. Dyspepsia improvement 3. Quality of life 4. Health-related dyspepsia costs 5. Adverse events	RCTs
Is empirical PPI therapy the most appropriate strategy for patients <60 years of age with dyspepsia that are <i>H. pylori</i> negative or remain symptomatic after eradication therapy?	Adult uninvestigated dyspepsia patients	Empirical PPI therapy	1. Placebo 2. Do nothing 3. H <sub>2</sub> RA 4. Prokinetic	1. Dyspepsia resolution 2. Dyspepsia improvement 3. Quality of life 4. Health-related dyspepsia costs 5. Adverse events	RCTs
Is empirical prokinetic therapy the most appropriate strategy for patients <60 years of age with dyspepsia that remain symptomatic after <i>H. pylori</i> test and treat and empirical PPI?	Adult uninvestigated dyspepsia patients	Prokinetic	Placebo or do nothing/antacids	1. Dyspepsia resolution 2. Dyspepsia improvement 3. Quality of life 4. Adverse events	RCTs
Is empirical antidepressant therapy the most appropriate strategy for patients <60 years of age with dyspepsia after <i>H. pylori</i> test and treat and empirical PPI therapy?	Adult uninvestigated dyspepsia patients	Antidepressant therapy	Placebo or do nothing/antacids	1. Dyspepsia resolution 2. Dyspepsia improvement 3. Quality of life 4. Adverse events	RCTs
Is <i>H. pylori</i> eradication therapy in <i>H. pylori</i> -positive patients effective in reducing symptoms of FD?	Adult dyspepsia patients with predominant epigastric pain/discomfort and a normal EGD that are <i>H. pylori</i> positive	<i>H. pylori</i> eradication therapy	Placebo antibiotics	1. Dyspepsia resolution 2. Dyspepsia improvement 3. Quality of life 4. Health-related dyspepsia costs 5. Adverse events	RCTs
Is PPI therapy effective in reducing symptoms of FD?	Adult dyspepsia patients with predominant epigastric pain/discomfort and a normal EGD	PPI therapy	1. Placebo 2. H <sub>2</sub> RA 3. Prokinetic	1. Dyspepsia resolution 2. Dyspepsia improvement 3. Quality of life 4. Adverse events	RCTs
Is antidepressant therapy effective in reducing symptoms of FD?	Adult dyspepsia patients with predominant epigastric pain/discomfort and a normal EGD	Antidepressant therapy	Placebo or do nothing/antacids	1. Dyspepsia resolution 2. Dyspepsia improvement 3. Quality of life 4. Adverse events	RCTs
Is prokinetic therapy effective in reducing symptoms of FD?	Adult dyspepsia patients with predominant epigastric pain/discomfort and a normal EGD	Prokinetic therapy	Placebo or do nothing/antacids	1. Dyspepsia resolution 2. Dyspepsia improvement 3. Quality of life 4. Adverse events	RCTs
Are psychological therapies effective in reducing symptoms of FD?	Adult dyspepsia patients with predominant epigastric pain/discomfort and a normal EGD	Psychological therapy	Usual care or sham therapy	1. Dyspepsia resolution 2. Dyspepsia improvement 3. Quality of life 4. Adverse events	RCTs

EGD, upper GI endoscopy; FD, functional dyspepsia; GI, gastrointestinal; *H. pylori*, *Helicobacter pylori*; H<sub>2</sub>RA, H<sub>2</sub>-receptor antagonist; PICO, population, intervention, comparator, outcome; PPI, proton pump inhibitor; RCT, randomized controlled trial.

The quality of evidence was expressed as high (estimate of effect is unlikely to change with new data), moderate, low, or very low (estimate of effect is very uncertain) with objective reproducible criteria that determine how this is assessed that involves the risk of bias of the studies, evidence of publication bias, unexplained heterogeneity among studies, directness of the evidence and precision of the estimate of effect (20). A summary of the quality of evidence for the statements is given in **Tables 3–5**. The strength of recommendation was given as either strong (most patients should receive the recommended course of action) or conditional (many patients will have this recommended course of action but different choices may be appropriate for some patients and a greater discussion is warranted so each patient can arrive at a decision based on their values and preferences). The strength of recommendation is based on the quality of evidence, risks vs. benefits, patients' values and preferences, as well as costs (21). We used a modified Delphi approach to developing consensus based on the evidence with iterative discussion on the evidence for each statement by e-mail and phone calls with one face-to-face meeting. Voting on all statements was unanimous, including the strength or recommendation and quality of evidence. A summary of the recommendations is given in **Table 1**. Algorithms for suggested management of patients with undiagnosed dyspepsia and FD are given in **Figure 1** and **Figure 2**, respectively.

#### **STATEMENT 1. WE SUGGEST DYSPEPSIA PATIENTS AGED 60 OR OVER HAVE AN ENDOSCOPY TO EXCLUDE UPPER GASTROINTESTINAL NEOPLASIA**

##### **Conditional recommendation, very low quality evidence**

Gastric cancer is the third commonest cause of cancer mortality worldwide with nearly a million cases annually (22) and often presents with dyspepsia. Endoscopy can detect gastric cancer at an earlier stage (23) and therefore is advisable in patients at significant risk of this disease. Endoscopy can also diagnose esophageal adenocarcinoma, which has been increasing rapidly in North America although there is now evidence that the rising incidence is reaching a plateau (24). While endoscopy is the gold standard test for diagnosing malignancy, it is expensive and invasive with a small risk of serious morbidity and mortality (25,26). All guidelines have therefore recommended alternative approaches for management of dyspepsia in patients with low risk of malignancy. The risk of malignancy is predominantly related to age and so previous ACG guidelines (10) have suggested that routine endoscopy to investigate dyspepsia should only be performed in patients' aged 55 and over. We have raised this threshold further to >60 years of age as evidence that endoscopy was cost-effective at the 55-year-old threshold at that time was borderline in economic analyses (27). Furthermore, in the 10 years since then the age-specific incidence of gastric cancer has fallen further in the US and Canada (28,29) and studies have shown that the cost of endoscopy per case of upper GI cancer detected is prohibitive(30).

We have given this statement a conditional recommendation, as the quality of evidence is very low. The data mainly relate to national databases of upper GI cancer risk (28,29), case series on

early gastric cancer detection (23) and economic modeling (27). These types of data are indirect and often overestimate the benefit of endoscopy, so clinicians may treat a minority of patients over the age of 60 with empirical therapy provided they feel the risk of upper GI cancer malignancy is low. On the other hand, the risk of upper GI malignancy increases in those who were born and spent their childhood in certain geographical regions such as South East Asia and some countries in South America (31). In light of the conditional recommendation with the quality of evidence being low, the age threshold for endoscopy should be lowered in these patients, and possibly others, according to clinical judgment. In borderline cases the sex of the patient may be taken into consideration as age-adjusted upper GI cancer risk is about twice as high in men as it is in women (31). As with all guidelines, clinical decisions should be based on symptoms, patient concerns, physical examination findings, laboratory and radiologic studies, and data from the literature, when available.

#### **STATEMENT 2. WE DO NOT SUGGEST ENDOSCOPY TO INVESTIGATE ALARM FEATURES FOR DYSPEPSIA PATIENTS UNDER THE AGE OF 60 TO EXCLUDE UPPER GI NEOPLASIA**

##### **Conditional recommendation, moderate quality evidence**

Previous guidelines (10–12) have typically recommended upper GI endoscopy at any age when alarm features (e.g., weight loss, anemia, dysphagia, persistent vomiting) are present. However, a systematic review of seven studies evaluating over 46,000 dyspepsia patients undergoing upper GI endoscopy found that alarm features had limited value (32). Alarm features also had limited utility in detecting any organic pathology (malignancy, peptic ulcer disease, or esophagitis) (33). Individual alarm features such as weight loss, anemia, or dysphagia had sensitivities and specificities of ~66% with a positive likelihood ratio of 2.74 (95% CI=1.47–5.24) (31). This means that if a dyspepsia patient has an alarm feature they have a 2–3-fold risk of having underlying upper GI malignancy. However, the risk of a person <60 years old having malignancy is typically very low so, even with an alarm feature, the risk is still much <1% and it is very unlikely that endoscopy of all young patients with alarm features would be cost-effective. Data published since this systematic review have been administrative database studies that have confirmed that alarm features have a low positive predictive value and so are of limited value in stratifying patients for endoscopy (34–37). It should be noted that this guideline does not cover patients presenting with alarm features such as progressive dysphagia and/or weight loss in the absence of epigastric pain. Such patients do not meet definitions for dyspepsia and are out of the scope of this guideline. Similarly, this guideline does not cover epigastric pain presentations which suggest a pancreatic or biliary source (e.g., pain radiating to the back), which should generally prompt appropriate imaging such as ultrasound or CT. Further, alarm features not discussed above (e.g., jaundice) would clearly need to be investigated with tests other than endoscopy. Pancreatic cancer can present as epigastric pain and it would be sensible to exclude this diagnosis in patients



over the age of 60 presenting with new onset dyspepsia by combining endoscopy with an imaging modality that evaluates the pancreas such as abdominal ultrasound. In patients <60 years of age pancreatic cancer is rare and it is important to note that a systematic review of >57,000 dyspepsia patients <0.01% had pancreatic cancer (32). This is consistent with the low incidence of pancreatic cancer in the US population <60 years of age. The pre-test probability of pancreatic cancer, even in those presenting with dyspepsia, is likely to be very low in this population, and therefore we do not recommend routinely imaging the pancreas in younger patients with dyspepsia.

The quality of evidence is moderate as it is based on cross-sectional studies and there is some unexplained heterogeneity among studies. The recommendation is conditional as the group felt that a minority of patients <60 years of age with alarm features would warrant endoscopy, particularly if the feature was prominent (e.g., weight loss >20lb or rapidly progressive dysphagia) or if a combination of features were present. Current data have not evaluated severe symptoms or combinations of features, so the need for endoscopy needs to be evaluated on a case-by-case basis in these circumstances using clinical judgment. Risk also increases with age so the threshold to refer for upper GI endoscopy would be lower in a 58-year-old compared to a 28-year-old with dyspepsia and alarm features. Family history of upper GI malignancy would also factor into any endoscopy decision.

### STATEMENT 3. WE RECOMMEND DYSPEPSIA PATIENTS UNDER THE AGE OF 60 SHOULD HAVE A NON-INVASIVE TEST FOR *H. PYLORI*, AND THERAPY FOR *H. PYLORI* INFECTION IF POSITIVE

#### Strong recommendation, high quality evidence

Six trials (38–43) compared *H. pylori* test and treat with prompt upper GI endoscopy in 2,399 undiagnosed dyspepsia patients. Most trials followed patients for 1 year and there was no difference in terms of global dyspepsia symptoms at the end of follow up between *H. pylori* test and treat and prompt endoscopy (74 vs. 77%, respectively, continued to have symptoms) with a RR of remaining dyspeptic in the *H. pylori* test and treat compared to the endoscopy group of 0.94 (95% CI=0.84–1.04) (Appendix 2: Appendix Figure 1). Twenty-five percent of patients in the *H. pylori* test and treat arm had an upper GI endoscopy over a 1-year period compared with nearly all patients in the prompt endoscopy arm (Appendix 2: Appendix Figure 2). This was the main driver in the statistically significant cost saving in the *H. pylori* test and treat group (mean saving=\$402; 95% CI=\$329–\$475) (Appendix 2: Appendix Figure 3) (39–41,43,44). We suggest that clinicians allow at least 4 weeks before reassessing symptomatic response to *H. pylori* eradication therapy.

Two trials (45,46) involving 563 *H. pylori*-infected dyspepsia patients randomized participants to eradication therapy or placebo. There was a statistically significant benefit of *H. pylori* eradication therapy (RR remaining dyspeptic=0.81; 95% CI=0.70–0.94) with a NNT of seven (95% CI=5–14) (Appendix 2: Appendix Figure 4).

The other main comparator to *H. pylori* test and treat was empirical PPI therapy. There were four trials (43,47–49) involving 1,608 dyspepsia patients that compared these strategies with 1-year follow up. Overall 73% of patients had dyspepsia at the end of 1-year follow up in the *H. pylori* test and treat group vs. 78% in the PPI group. There was no statistically significant difference between the two strategies (RR=0.89; 95% CI=0.77–1.04) (Appendix 2: Appendix Figure 5). A systematic review (50) found there was a trend towards a reduction in cost for *H. pylori* test and treat compared to empirical PPI therapy, but this was not statistically significant. The trend for both benefit and costs favored *H. pylori* test and treat compared to empirical PPI and, therefore, the group felt this was the preferred initial strategy with acid suppression reserved for those who were *H. pylori* negative or who continued to have symptoms despite eradication therapy.

The quality of evidence was high as the findings were robust with narrow CIs. All trials were high risk of bias as blinding was not possible with this type of comparison. The impact of reduction of costs and endoscopy was very strong and there was little clinically important heterogeneity among studies. The randomized trials that have evaluated *H. pylori* test and treat all reported *H. pylori* infection rates that were between 20 and 30% (refs 38–44,47–49). A previous guideline (12) suggested that PPI therapy might be the appropriate first line approach when *H. pylori* prevalence rates are <15% in the population being tested. We felt that it is often difficult to know what the *H. pylori* prevalence is in the local population and even with very low rates of infection test and treat is likely to be the most cost-effective first line strategy as randomized trials data suggests that this approach will reduce gastric cancer rates in those infected (51,52).

### STATEMENT 4. WE RECOMMEND DYSPEPSIA PATIENTS UNDER THE AGE OF 60 SHOULD HAVE EMPIRICAL PPI THERAPY IF THEY ARE *H. PYLORI*-NEGATIVE OR WHO REMAIN SYMPTOMATIC AFTER *H. PYLORI* ERADICATION THERAPY

#### Strong recommendation, high quality evidence

There were six randomized controlled trials (RCTs) (53–58) evaluating 2,709 dyspepsia patients that compared PPI therapy with placebo or antacid therapy. Overall dyspepsia symptoms were present in 50% of the PPI group vs. 73% of the placebo group (RR remaining dyspeptic on PPI=0.75; 95% CI=0.64–0.88) (Appendix 2: Appendix Figure 6) with an NNT of six (95% CI=4–11). The quality of evidence was high as, although some trials had an unclear risk of bias, the effect was strong and most studies reported a statistically significant effect of PPI therapy on symptoms.

The alternative approach to PPI therapy is to reduce acid production with an H<sub>2</sub>-receptor antagonist (H<sub>2</sub>RA). There were 7 RCTs (53,57,59–63) evaluating 2,456 dyspepsia patients comparing these two approaches. There was no statistically significant difference between PPI and H<sub>2</sub>RA in providing symptom relief (RR=0.93; 95% CI=0.76–1.16) with a large amount of heterogeneity among studies (*I*<sup>2</sup>=91% (Appendix 2: Appendix Figure 7). Four trials (53,59,60,62) had a significant effect in favor of PPI, two trials

**Table 3. Summary or findings of studies evaluating alarm features**

Outcome	No of studies (No of patients)	Study design	Factors that may decrease quality of evidence				Test accuracy QoE		
			Risk of bias	Indirectness	Inconsistency	Imprecision		Publication bias	Effect per 1,000 patients tested
True positives (patients with upper GI cancer)	7 studies 150 patients	Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Serious <sup>a</sup>	Not serious	None	2 (2–2)	⊕⊕⊕⊕ Moderate
False negatives (patients incorrectly classified as not having upper GI cancer)								1 (1–1)	–
True negatives (patients without upper GI cancer)	7 studies 46,011 patients	Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Serious <sup>a</sup>	Not serious	None	658 (548–788)	⊕⊕⊕⊕ Moderate
False positives (patients incorrectly classified as having upper GI cancer)								339 (209–449)	–

CI, confidence interval; GI, gastrointestinal.  
 Sensitivity: 0.67 (95% CI: 0.54–0.83).  
 Specificity: 0.66 (95% CI: 0.55–0.79).  
 Prevalence: 0.3%.  
<sup>a</sup>Significant unexplained heterogeneity between studies.

(57,63) showed no significant difference between both groups and one trial showed a benefit of H<sub>2</sub>RA (ref. 61). This trial (61) evaluated an H<sub>2</sub>RA not available in the West. It is not biologically plausible that H<sub>2</sub>RA would be more effective than PPI therapy; if this trial is excluded there is a significant benefit of PPI over H<sub>2</sub>RA (RR remaining dyspeptic=0.81; 95% CI=0.72–0.91). There is not a major difference in cost between H<sub>2</sub>RA and PPI therapy and the group felt the balance of evidence supported empirical PPI over H<sub>2</sub>RA therapy.

There were five RCTs (43,64–67) involving 1,752 dyspepsia patients that found no significant difference in dyspepsia symptoms between prompt endoscopy and empirical acid suppression with PPI or H<sub>2</sub>RA therapy (RR=1.00; 95% CI=0.94–1.05) (**Appendix 2: Appendix Figure 8**).

The evidence was graded as high as there were no concerns regarding heterogeneity, publication bias, imprecision, or risk of bias in the estimate of effect. The evidence is somewhat indirect as we are recommending this for dyspepsia patients who are *H. pylori*-negative or are symptomatic after eradication therapy. The trials were from an unselected group of dyspepsia patients but most were *H. pylori*-negative and we felt this minor degree of indirectness of the evidence was insufficient to reduce the quality of the trials. It should also be noted that the PPI trials used once-daily standard dosing. It is unlikely that higher doses of PPI will increase benefit in dyspepsia.

**STATEMENT 5. WE SUGGEST DYSPEPSIA PATIENTS UNDER THE AGE OF 60 NOT RESPONDING TO PPI OR *H. PYLORI* ERADICATION THERAPY SHOULD BE OFFERED PROKINETIC THERAPY**

**Conditional recommendation very low quality evidence**

There is a relative paucity of data evaluating prokinetic therapy in the treatment of undiagnosed dyspepsia. There were no randomized studies comparing prokinetic therapy with placebo. There were three trials (57,62,66) that compared PPI with prokinetic therapy in 680 dyspepsia patients. Follow up was from 4 to 52 weeks and there was a trend towards PPI being more effective than prokinetic therapy (RR=0.78; 0.60–1.02, *P*=0.06) (**Appendix 2: Appendix Figure 9**) but this did not achieve statistical significance. Two trials (57,62) showed PPI therapy was superior and one (66) reported no difference.

All trials were high risk of bias and the effect was uncertain so the quality of the evidence was rated very low. We felt that prokinetic therapy should be offered after *H. pylori* test and treat and/or PPI therapy has failed as PPI therapy is more effective in gastroesophageal reflux disease (68) and peptic ulcer disease (69) and has greater efficacy in FD using indirect comparisons of randomized data (see below). Furthermore, the prokinetics that were evaluated in randomized trials (cisapride and mosapride) are not available in most countries worldwide. Given risks of potential side effects with prokinetics, they should be used at the lowest effective dose and consistent with country specific safety recommendations (e.g., metoclopramide use less than 12 weeks (70), domperidone dose 30 mg daily or less (71)).

**Table 4. Summary of findings table for management strategies in uninvestigated dyspepsia**

No of studies	Quality assessment					No of patients		Effect		Quality	Importance	
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	Relative (95% CI)			Absolute (95% CI)
<i>H. pylori</i> test and treat vs. endoscopy: dyspepsia outcome (follow up: median 1 years; assessed with: questionnaire)												
6	Randomized trials	Serious <sup>a</sup>	Not serious	Not serious	Not serious	None	896/1,219 (73.5%)	904/1,180 (76.6%)	RR 0.94 (0.84–1.04)	46 fewer per 1,000 (from 31 more to 123 fewer)	⊕⊕⊕⊕ Moderate	Critical
<i>H. pylori</i> test and treat vs. endoscopy: health-related dyspepsia costs (US \$) (follow up: median 1 years; assessed with: questionnaire)												
5	Randomized trials	Serious <sup>a</sup>	Not serious	Not serious	Not serious	Strong association	893	878	–	MD 402 s.d. more (329 more to 475 more)	⊕⊕⊕⊕ High	Critical
PPI therapy vs. placebo: dyspepsia outcome (follow up: range 2–8 weeks)												
6	Randomized trials	Not serious	Serious <sup>b</sup>	Not serious	Not serious	Strong association	743/1,500 (49.5%)	877/1,209 (72.5%)	RR 0.75 (0.64–0.88)	181 fewer per 1,000 (from 87 fewer to 261 fewer)	⊕⊕⊕⊕ High	Critical
PPI vs. prokinetic therapy: dyspepsia outcome (follow up: range 2–8 weeks)												
3	Randomized trials	Not serious	Serious <sup>b</sup>	Not serious	Very serious	None	250/366 (68.3%)	314/279 (112.5%)	RR 0.78 (0.60–1.02)	248 fewer per 1,000 (from 23 more to 450 fewer)	⊕⊕⊕⊕ Very low	Critical
TCA therapy: dyspepsia outcome (follow up: range 2–8 weeks)												
3	Randomized trials	Not serious	Not serious	Serious <sup>c</sup>	Serious <sup>d</sup>	None	77/170 (45.3%)	104/169 (61.5%)	RR 0.74 (0.61–0.91)	160 fewer per 1,000 (from 55 fewer to 240 fewer)	⊕⊕⊕⊕ Low	Critical

CI, confidence interval; FD, functional dyspepsia; MD, mean difference; PPI, proton pump inhibitor; RR, risk ratio; TCA, tricyclic antidepressant.

<sup>a</sup>All trials high risk of bias as blinding not possible.

<sup>b</sup>Significant unexplained heterogeneity with *I*<sup>2</sup>>50%.

<sup>c</sup>Patients had FD and not uninvestigated dyspepsia. We are assuming most patients will have FD.

<sup>d</sup>95% CI are relatively wide as only based on three studies.

**Table 5. Summary of findings table for interventions for FD**

No of studies	Study design	Quality assessment					No of patients		Effect		Quality	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	Relative (95% CI)	Absolute (95% CI)		
<i>H. pylori</i> eradication vs. placebo antibiotics in <i>H. pylori</i> +ve FD (follow up: range 3–12 months)												
22	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	1,767/2,604 (67.9%)	1,751/2,292 (76.4%)	RR 0.91 (0.88–0.94)	69 fewer per 1,000 (from 46 fewer to 92 fewer)	⊕⊕⊕⊕ High	Critical
PPI therapy vs. placebo (follow up: range 2–4 weeks)												
15	Randomized trials	Not serious	Serious <sup>a</sup>	Not serious	Not serious	None	2,332/3,621 (64.4%)	1,293/1,777 (72.8%)	RR 0.83 (0.77–0.89)	124 fewer per 1,000 (from 80 fewer to 167 fewer)	⊕⊕⊕⊕ Moderate	Critical
TCA therapy vs. placebo (follow up: range 2–12 weeks)												
3	Randomized trials	Not serious	Not serious	Not serious	Serious <sup>b</sup>	None	77/170 (45.3%)	104/169 (61.5%)	RR 0.74 (0.61–0.91)	160 fewer per 1,000 (from 55 fewer to 240 fewer)	⊕⊕⊕⊕ Moderate	Critical
Prokinetic therapy vs. placebo (follow up: range 2–8 weeks)												
26	Randomized trials	Not serious	Serious <sup>a</sup>	Not serious	Serious <sup>c</sup>	Publication bias strongly suspected <sup>d</sup>	3,430/5,123 (67.0%)	2,815/3,665 (76.8%)	RR 0.92 (0.88–0.97)	61 fewer per 1,000 (from 23 fewer to 92 fewer)	⊕⊕⊕⊕ Very low	Critical
Psychological therapies vs. usual care (follow up: range 4–12 weeks)												
4	Randomized trials	Very serious <sup>e</sup>	Serious <sup>a</sup>	Not serious	Serious <sup>f</sup>	Strong treatment effect	125/394 (31.7%)	243/395 (61.5%)	RR 0.53 (0.44–0.65)	283 fewer per 1,000 (from 203 fewer to 345 fewer)	⊕⊕⊕⊕ Very low	Critical

CI, Confidence interval; FD, functional dyspepsia; PPI, proton pump inhibitor; RR, risk ratio; TCA, tricyclic antidepressant.

<sup>a</sup>Unexplained heterogeneity with  $I^2 > 50\%$ .

<sup>b</sup>Wide 95% CI as based on three trials.

<sup>c</sup>Various prokinetics evaluated and none available in US or Canada—those that have a statistically significant effect show very modest efficacy with 95% CI close to 1.0.

<sup>d</sup>Strong funnel plot asymmetry with small trials showing large effect and many large trials negative.

<sup>e</sup>Studies not blinded and outcome subjective.

<sup>f</sup>Wide 95% CI and only two RCTs for any type of intervention.



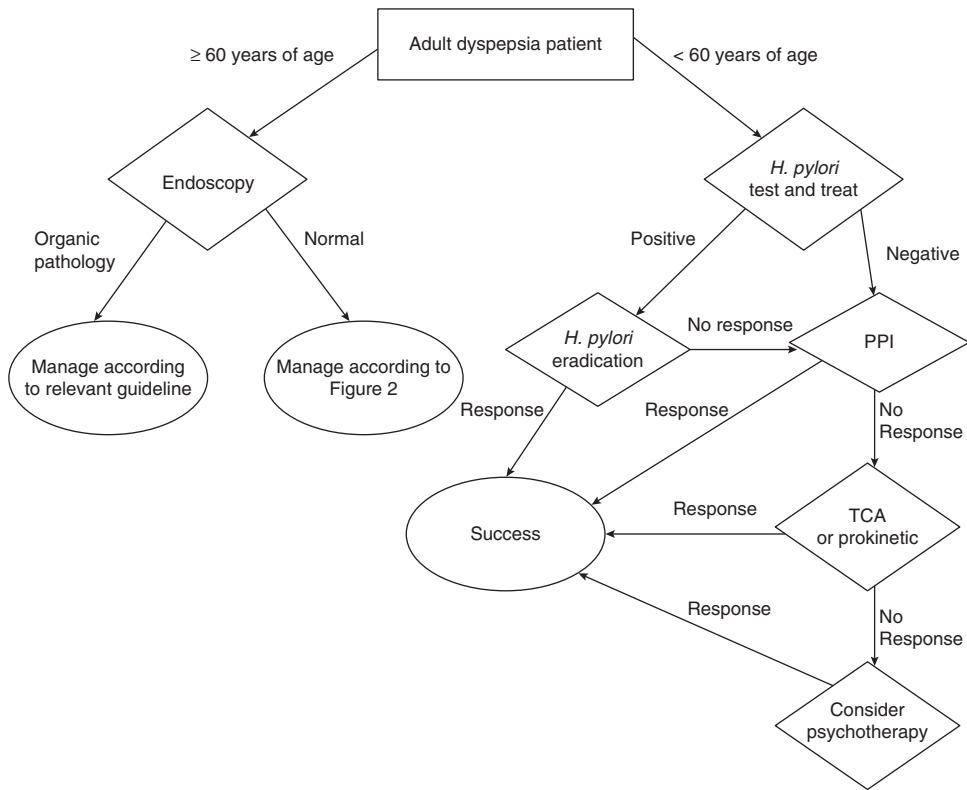


Figure 1. Algorithm for the management of undiagnosed dyspepsia.

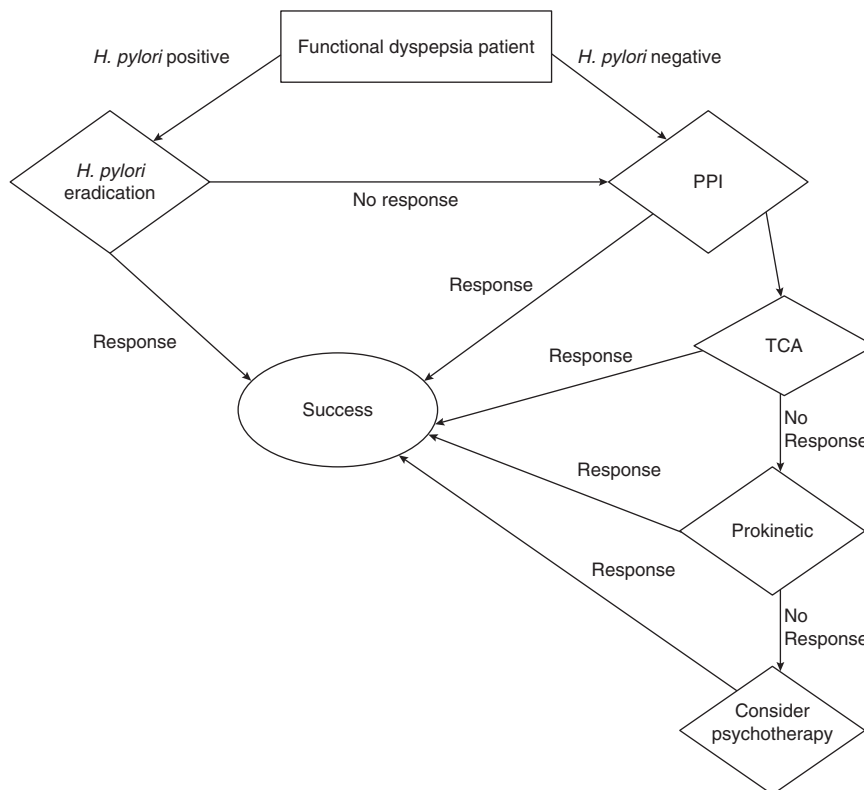


Figure 2. Algorithm for the treatment of functional dyspepsia.

**STATEMENT 6. WE SUGGEST DYSPEPSIA PATIENTS UNDER THE AGE OF 60 NOT RESPONDING TO PPI OR *H. PYLORI* ERADICATION THERAPY SHOULD BE OFFERED TRICYCLIC ANTIDEPRESSANT THERAPY**

**Conditional recommendation low quality evidence**

There are no randomized trials of antidepressant therapies in undiagnosed dyspepsia. A systematic review (72) identified 13 trials involving 1,241 patients with FD that evaluated psychotropic drugs compared to placebo. The review identified three trials that evaluated TCA therapy and these drugs had a significant effect in reducing dyspepsia symptoms (RR=0.74; 95% CI=0.61–0.91). No effect was seen with serotonin reuptake inhibitor therapy. The quality of evidence is low as there is no study evaluating undiagnosed dyspepsia. The results are therefore indirectly applied to this population with the assumption that most dyspepsia patients in North America will have FD (73). TCAs are unlikely to have a major impact on peptic ulcer disease or gastro-esophageal reflux disease and so their efficacy in the general dyspepsia population is likely to be lower than estimated in the systematic review. The recommendation is conditional based on the low quality of evidence, the adverse events associated with TCAs (72) and considerations that some patients will not like the perceived stigma of taking an antidepressant. The decision to use TCAs will therefore be made on a case-by-case basis and the group did not find a preference in the order in which prokinetic or TCA therapy is prescribed.

**STATEMENT 7. WE RECOMMEND FUNCTIONAL DYSPEPSIA PATIENTS THAT ARE *H. PYLORI* POSITIVE SHOULD BE PRESCRIBED THERAPY TO TREAT THE INFECTION**

**Strong recommendation, high quality evidence**

Patients who have an endoscopy with normal findings and predominant epigastric pain are considered to have FD. A positive diagnosis of FD can also be made without endoscopy using clinical symptoms and history (14). Patients with a normal endoscopy should have gastric biopsies to assess for the presence of *H. pylori* infection if prior non-invasive testing has not been performed. There are a number of biologically plausible reasons why *H. pylori* infection may lead to dyspepsia symptoms in FD (74). We identified 22 RCTs (75–96) evaluating 4,896 *H. pylori*-positive FD patients that compared eradication therapy with placebo antibiotics. Follow up was for 3–12 months and all gave outcome in terms of global improvement in dyspepsia symptoms. Overall 1,767/2,604 (67.9%) patients in the *H. pylori* eradication therapy group had persistence of dyspepsia symptoms compared with 1,751/2,292 (76.4%) in the control group. There was a statistically significant impact of *H. pylori* eradication on dyspepsia symptoms (RR dyspepsia remaining=0.91; 95% CI=0.88–0.94;  $P<0.00001$ ) with no significant heterogeneity ( $\chi^2=20.5$ ,  $P=0.49$ ,  $I^2=0\%$ ) (Appendix 2: Appendix Figure 10). There was no funnel plot asymmetry and the NNT was 12.5 (95% CI=10–20).

The quality of evidence is high as the subset of low risk of bias trials gave a similar statistically significant result and there is no

unexplained heterogeneity among studies and no evidence of publication bias. The recommendation is strong as the approach is cost-effective (97) and adverse events associated with antibiotics are usually mild. Although the impact on dyspepsia symptoms is modest, *H. pylori* eradication may also reduce future risk of gastric cancer and peptic ulcer disease and the benefits of this approach clearly outweigh the harms of antibiotic prescribing. It is worth noting that the evidence suggests that antibiotics reduce dyspepsia symptoms and the assumption is that this is due to eradicating *H. pylori* infection. It is possible that the efficacy relates to treating other infectious agents (98) that might cause dyspepsia but this nuance does not change the recommendation that *H. pylori*-positive FD patients should be offered eradication therapy.

**STATEMENT 8. WE RECOMMEND FUNCTIONAL DYSPEPSIA PATIENTS WHO ARE *H. PYLORI*-NEGATIVE OR WHO REMAIN SYMPTOMATIC DESPITE ERADICATION OF THE INFECTION SHOULD BE TREATED WITH PPI THERAPY**

**Strong recommendation, moderate quality evidence**

There is some evidence that a subset of FD may relate to heightened sensitivity to acid (99). We identified 15 RCTs in 14 papers (100–113) evaluating 5,853 FD patients that compared PPI therapy at standard and/or low dose with placebo. Follow up was for 2–8 weeks and all reported outcome in terms of global improvement in dyspepsia symptoms. We combined low and standard dose PPI arms as the comparison between the two revealed no significant difference. Overall 2,724/3,916 (69.6%) patients in the PPI group had persistence of dyspepsia symptoms compared with 1,457/1,937 (75.2%) in the control group. There was a statistically significant impact of PPI therapy on dyspepsia symptoms (RR dyspepsia remaining=0.87; 95% CI=0.82–0.94;  $P<0.00001$ ) (Appendix 2: Appendix Figure 11) with a NNT of 10 (95% CI=7–20).

Randomized trials comparing alternatives to PPI therapy were considered. There were two RCTs (100,114) comparing PPI to  $H_2RA$  in 740 FD patients with no significant difference between the two therapies (RR=1.27; 95% CI=0.83–1.94). There is insufficient data to have confidence that  $H_2RA$  is not inferior to PPI therapy and PPI therapy results in more profound acid suppression. There were four RCTs (115–118) involving 892 FD patients comparing PPI with prokinetics. There was a statistically significant difference between the two therapies in favor of PPI therapy (RR dyspepsia remaining=0.90; 95% CI=0.81–1.00,  $P=0.04$ ) (Appendix 2: Appendix Figure 12).

Data suggest that there is no value in doubling the dose of PPI therapy so the drug should be discontinued if the patient does not respond after 8 weeks of standard dose, once-daily therapy. Subgroup analysis suggests that those patients who have more prominent heartburn-related symptoms respond better to PPI therapy (119) but there is no evidence that epigastric pain syndrome responds better than postprandial distress syndrome type dyspepsia (115). We therefore do not recommend using the type of symptom in FD to guide treatment choice. The quality

of the evidence was moderate as there was some unexplained heterogeneity in the data. The recommendation was strong as PPI therapy is well tolerated and inexpensive.

We evaluated recent concerns regarding the long-term risk of PPI therapy, among which hip fracture, community-acquired pneumonia, *C. difficile* infection, electrolyte disturbances, and dementia have been hypothesized (120). However, we feel the most likely explanation for these associations is residual confounding (121) and even if the associations were causal, the number needed to harm was >1,000 in most cases (122) and the benefits outweighed any known harms. However, PPI therapy should be stopped if it is no longer providing benefit and patients should not have long-term PPI therapy without attempts to withdraw it every 6–12 months, consistent with US FDA guidance (123)

#### STATEMENT 9. WE RECOMMEND FUNCTIONAL DYSPEPSIA PATIENTS NOT RESPONDING TO PPI OR *H. PYLORI* ERADICATION THERAPY (IF APPROPRIATE) SHOULD BE OFFERED TRICYCLIC ANTIDEPRESSANT THERAPY

##### Conditional recommendation, moderate quality evidence

Antidepressant therapies have been shown in randomized trials to reduce symptoms in irritable bowel syndrome (124). There is a large overlap between irritable bowel syndrome and FD (125) so it is plausible that antidepressants will also be effective for dyspepsia symptoms. A systematic review (72) identified 13 RCTs evaluating psychotropic drugs in FD. There were three trials (126–128) involving 339 FD patients comparing TCAs with placebo. There was a statistically significant effect in reducing dyspepsia symptoms (RR=0.74; 95% CI=0.61–0.91) with an NNT of six (95% CI=6–18). There were two trials (128,129) involving 388 FD patients comparing SSRIs with placebo. There was no statistically significant effect of SSRI therapy on dyspepsia symptoms (RR=1.01; 95% CI=0.89–1.15) (72).

The quality of evidence was moderate as there was some uncertainty around the estimate of effect of TCAs as the 95% CI were wide. The recommendation was conditional as TCAs are associated with adverse events (which include constipation, dry mouth, urinary retention, and somnolence) (72) and a significant proportion of patients might prefer not to take antidepressant medication. In contrast to Statements 5 and 6 above, it should be noted that we recommend TCA before prokinetic for treatment of FD based on the superior evidence for TCA in this indication.

#### STATEMENT 10. WE SUGGEST FUNCTIONAL DYSPEPSIA PATIENTS NOT RESPONDING TO PPI, *H. PYLORI* ERADICATION THERAPY OR TRICYCLIC ANTIDEPRESSANT THERAPY SHOULD BE OFFERED PROKINETIC THERAPY

##### Conditional recommendation, very low quality evidence

Patients with FD often have disorders of gastric motility (130) and many pharmacological agents have been developed to improve gastric emptying (131). Prokinetics have been studied exten-

sively in FD and we identified 26 randomized trials in 23 papers (132–154) involving 8,788 FD patients. There was a statistically significant effect of prokinetic therapy in reducing global symptoms of FD with a RR of remaining dyspeptic in the prokinetic group of 0.92 (95% CI=0.88–0.97) (**Appendix 2: Appendix Figure 13**) with a NNT of 12.5 (95% CI=8–25). None of the prokinetic therapies that were eligible to review for this guideline is available in US, Canada, or Europe. There are no clinical trials with metoclopramide in FD.

There were seven trials (155–161) involving 263 patients with upper GI symptoms that evaluated domperidone. These were all excluded, as they did not meet *a priori* eligibility criteria. The usual reason was that patients had a barium meal rather than endoscopy and/or a non-standard definition of dyspepsia was used. Nevertheless we synthesized these data, as domperidone is available in Canada and some other countries although not in the US. Overall there was a statistically significant effect on symptoms (RR remaining symptomatic with domperidone=0.71; 95% CI=0.53–0.97) (**Appendix 2: Appendix Figure 14**) with a NNT of 3 (95% CI=2–8).

The quality of evidence was graded as very low as all of the domperidone data had unclear or high risk of bias and none met eligibility criteria. All other prokinetic data had significant unexplained heterogeneity and there was evidence of publication bias, small positive studies driving the result and larger trials showing little or no treatment effect (Egger test for bias— $P=0.004$ ). Furthermore some prokinetics have significant risk of adverse events (131) with metoclopramide being associated with dystonia, parkinsonism-type movements, and/or tardive dyskinesia while domperidone may cause QT prolongation which in turn could increase the risk of serious arrhythmias in those with pre-existing cardiac conditions.

#### STATEMENT 11. WE SUGGEST FUNCTIONAL DYSPEPSIA PATIENTS NOT RESPONDING TO DRUG THERAPY SHOULD BE OFFERED PSYCHOLOGICAL THERAPIES

##### Conditional recommendation, very low quality evidence

There are a large number of trials suggesting psychological therapies are effective in irritable bowel syndrome (124) although the quality of these data is very low. A previous systematic review (162) of psychological therapies in FD suggested the number of trials were limited so no firm conclusions could be made. We have updated this review and have now identified a total of 12 RCTs (163–174) involving 1,563 FD patients. All trials reported a statistically significant benefit of psychological therapies over control, which was most commonly usual management. These studies reported a variety of psychological interventions; the commonest approaches were cognitive behavioral therapy or other various forms of psychotherapy. Only four papers (165,169,172,174) described the outcome in terms of a dichotomous improvement in dyspepsia symptoms in 789 FD patients. These studies suggested that there was a significant benefit of psychological therapies in reducing dyspepsia symptoms (RR=0.53; 95% CI=0.44–0.65) (**Appendix 2: Appendix Figure 15**) with a NNT of three (95% CI=3–4).

The quality of the data is very low despite a reasonably dramatic effect on reducing dyspepsia symptoms. The studies were all high risk of bias as there was no blinding and this is important given the outcome of dyspepsia improvement is subjective. There was unexplained heterogeneity among studies and many used different forms of psychological therapy so there is a lack of precision around the estimate of effect for any given type of psychological intervention. The recommendation was conditional as the quality of the data was very low, may be expensive, and requires significant time and motivation from the patient.

**STATEMENT 12. WE DO NOT RECOMMEND THE ROUTINE USE OF COMPLEMENTARY AND ALTERNATIVE MEDICINES FOR FUNCTIONAL DYSPEPSIA**

**Conditional recommendation, very low quality evidence**

Complementary and alternative medicines (CAM) are used by about 20% of the general population for gastrointestinal symptoms (175). The proportion of secondary and tertiary care patients with FD taking CAM may be even higher. These interventions have been reviewed (131) and there are numerous proposed herbal remedies as well as other approaches. Many of these have been subject to randomized trials but the approaches are too diverse to draw any definitive conclusions. For example, one qualitative review (176) identified 26 CAM methods for treating FD. One of the largest single trials relates to STW 5, a herbal preparation containing extracts of bitter candy tuft, matricaria flower, peppermint leaves, caraway, licorice root, and lemon balm. 315 patients with FD were randomized to STW 5 or placebo for 8 weeks (177) and there was a statistically significant benefit for the active treatment but this was only marginal (Gastrointestinal Symptoms Score improved by  $6.9 \pm 4.8$  in the STW 5 group compared with  $5.9 \pm 4.3$ ,  $P=0.04$ ) and it is unclear whether this difference was clinically meaningful. A systematic review (178) of Chinese herbal medicine in FD identified 13 trials involving 1,153 patients. The review concluded that there was a signal that Chinese herbal medicine may improve FD symptoms but the trials were of very poor methodological quality. Similarly, a Cochrane review (179) of acupuncture in FD identified seven studies involving 542 FD patients. Again the authors felt that the data were of very low quality and concluded it was unclear whether acupuncture was effective in FD. CAM may be appropriate for individual patients interested in exploring these approaches provided they are aware that there is insufficient evidence to determine the benefit or risk of these interventions.

**STATEMENT 13. WE RECOMMEND AGAINST ROUTINE MOTILITY STUDIES FOR PATIENTS WITH FUNCTIONAL DYSPEPSIA**

**Conditional recommendation, very low quality evidence**

The diagnosis and treatment of FD can be challenging because symptoms develop due to a number of different pathophysiologic processes (12,180–182). Abnormal gastric accommodation has

been identified in up to 40% of patients with FD (12,180). However, this can be accurately identified with only two specialized motility studies (i.e., gastric barostat or single-photon emission computed tomography), neither of which is readily available (183). Delayed gastric emptying, using either scintigraphic tests or breath tests, has been identified in up to 30% of patients with FD, although the extent of this delay is usually mild (12,180,182). A recent, large-multicenter trial, using a validated 4-h solid phase gastric-emptying scan protocol with all studies read at one center, found that 21% of patients meeting Rome II criteria for FD had delayed gastric emptying (128). Symptoms of FD may also arise due to a prior infection (viral, bacterial, protozoal), visceral hypersensitivity, medications, duodenal eosinophilia, and abnormal or excess feedback from the upper small intestine (180,181,184). Unfortunately, however, identifying the abnormal pathophysiologic mechanisms that underlie the development of FD symptoms has not directly altered treatment strategies. For example, several studies have demonstrated a lack of relationship between FD symptoms and gastric emptying (149,185,186). Since tests to measure gastric accommodation are not readily available (barostat and single-photon emission computed tomography) or expensive, invasive and uncomfortable (barostat), and because delays in gastric emptying are not accurately related to symptoms, routine motility tests for patients with FD are not recommended.

**STATEMENT 14. WE SUGGEST MOTILITY STUDIES FOR SELECTED PATIENTS WITH FUNCTIONAL DYSPEPSIA WHERE GASTROPARESIS IS STRONGLY SUSPECTED**

**Conditional recommendation, very low quality evidence**

Gastroparesis can be diagnosed using a combination of symptoms (e.g., nausea, vomiting, abdominal pain, early satiety, bloating), an upper endoscopy not showing evidence of mechanical obstruction, and a delay in gastric emptying using a 4-h solid phase gastric-emptying scan (187). FD can be diagnosed using a combination of symptoms (e.g., upper abdominal pain, nausea, vomiting, early satiety, bloating) and a normal upper endoscopy (14). Although generally thought of as distinct, there is significant overlap in these two disorders and they likely represent part of a spectrum of gastric sensorimotor disorders (182). As noted, most patients (70–80%) with FD have normal gastric emptying; thus, routine motility testing is not required. In FD patients with delayed gastric emptying, the degree of delay is usually mild (10–20% of material remaining at 4h) (128). The occasional FD patient with persistent symptoms of nausea and vomiting may have a marked delay in gastric emptying (188,189), and identifying this could potentially lead to a change in therapy. Unfortunately, there is no data from RCTs to answer the question of how medical management changes if a marked delay in gastric emptying is identified. The patient with daily or intractable vomiting may have gastroparesis rather than FD and should be investigated appropriately. We felt that a 4-h solid phase gastric-emptying scan should be performed in FD patients with predominant symptoms of severe nausea and vomiting who fail empiric therapy.



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## CONFLICT OF INTEREST

**Guarantor:** Paul Moayyedi, MB, ChB, PhD, MPH, FACC.

**Specific author contributions:** All authors contributed to the development of the guideline statements, interpretation of the evidence for each statement and the writing of the article.

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**Potential competing interests:** Paul Moayyedi has accepted speaker fees from Allergan and Abbvie. He has been on advisory boards for Allergan, Shire and Salix pharmaceuticals. He has received research funds from Allergan and Takeda. Colin Howden is a consultant for Allergan, Aralez, Ironwood, Otsuka, SynteractHCR, Takeda and US World Meds. Christopher N. Andrews has honoraria from Allergan, Abbvie, Pendopharm, Lupin, and Medtronic; research support from Janssen and HPI Pharma; and is Director of Callitas Pharma. Robert Enns has no conflicts. Nimish Vakil is a consultant for AstraZeneca, Ironwood, Restech, Yuhan, Allergan, Otsuka, US World Meds and Actavis. Brian E. Lacy is on the advisory board for Ironwood, Covidien, and Salix, and has received research support from Covidien.

## REFERENCES

- Hoffer SE. Cicero's stomach: political indignation and the use of repeated allusive expressions in Cicero's correspondence. In: Morello R, Morrison AD (eds) *Ancient Letters: Classical and Late Antique Epistolography*. Oxford University Press, Oxford, UK, 2007.
- Whiting S. *Memoirs of a Stomach*. W.E. Painter: London, UK, 1853.
- Baron JH, Watson F, Sonnenberg A. Three centuries of stomach symptoms. *Aliment Pharmacol Ther* 2006;24:821–9.
- Ford AC, Marwaha A, Sood R *et al.* Global prevalence of, and risk factors for, uninvestigated dyspepsia: a meta-analysis. *Gut* 2015;64:1049–57.
- Ford AC, Forman D, Bailey AG *et al.* Effect of dyspepsia on survival: a longitudinal 10-year follow up study. *Am J Gastroenterol* 2012;107:912–21.
- Ford AC, Forman D, Bailey AG *et al.* Initial poor quality of life and new onset of dyspepsia: results from a longitudinal 10-year follow-up study. *Gut* 2007;56:321–7.
- Veldhuyzen van Zanten S, Wahlqvist P, Talley NJ *et al.* Randomised clinical trial: the burden of illness of uninvestigated dyspepsia before and after treatment with esomeprazole—results from the STARS II study. *Aliment Pharmacol Ther* 2011;34:714–23.
- Lacy BE, Weiser KT, Kennedy AT *et al.* Functional dyspepsia: the economic impact to patients. *Aliment Pharmacol Ther* 2013;38:170–7.
- Moayyedi P, Mason J. Clinical and economic consequences of dyspepsia in the community. *Gut* 2002;50(suppl 4):10–12.
- Talley NJ, Vakil N. Guidelines for the management of dyspepsia. *Am J Gastroenterol* 2005;100:2324–37.
- Veldhuyzen van Zanten SJ, Bradette M, Chiba N *et al.* Evidence-based recommendations for short- and long-term management of uninvestigated dyspepsia in primary care: an update of the Canadian Dyspepsia Working Group (CanDys) clinical management tool. *Can J Gastroenterol* 2005;19:285–303.
- Talley NJ, Vakil NB, Moayyedi P. American gastroenterological association technical review on the evaluation of dyspepsia. *Gastroenterology* 2005;129:1756–80.
- Colin-Jones DG, Bloom B, Bodemar G *et al.* Management of dyspepsia: report of a working party. *Lancet* 1988;331:576–9.
- Stanghellini V, Chan FKL, Hasler WL *et al.* Gastrointestinal disorders. *Gastroenterology* 2016;150:1380–92.
- Tack J, Talley NJ, Camilleri M *et al.* Functional gastroduodenal disorders. *Gastroenterology* 2006;130:1466–79.
- Vakil N, Halling K, Ohlsson L *et al.* Symptom overlap between postprandial distress and epigastric pain syndromes of the Rome III dyspepsia classification. *Am J Gastroenterol* 2013;108:767–74.
- Katz PO, Gerson LB, Vela MF. Diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol* 2013;108:308–28.
- Fallone CA, Chiba N, van Zanten SV *et al.* The Toronto consensus for the treatment of *Helicobacter pylori* infection in adults. *Gastroenterology* 2016;151:51–69.
- Guyatt GH, Oxman AD, Vist G *et al.* Rating quality of evidence and strength of recommendations GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–6.
- Guyatt GH, Oxman AD, Kunz R *et al.* Rating quality of evidence and strength of recommendations: What is "quality of evidence" and why is it important to clinicians? *BMJ* 2008;336:995–8.
- Guyatt GH, Oxman AD, Kunz R *et al.* Rating quality of evidence and strength of recommendations: going from evidence to recommendations. *BMJ* 2008;336:1049–51.
- GLOBCAN project, International Agency for Research on Cancer. <http://globocan.iarc.fr/old/FactSheets/cancers/stomach-new.asp>. Accessed on 11 May 2016.
- Spahos T, Hindermarsh A, Cameron E *et al.* Endoscopy waiting times and impact of the two week wait scheme on diagnosis and outcome of upper gastrointestinal cancer. *Postgrad Med J* 2005;81:728–30.
- Pohl H, Sirovich B, Welch HG. Esophageal adenocarcinoma incidence: are we reaching the peak? *Cancer Epidemiol Biomarkers Prev* 2010;19:1468–70.
- Quine MA, Bell GD, McCloy RF *et al.* Prospective audit of upper gastrointestinal endoscopy in two regions of England: safety, staffing and sedation methods. *Gut* 1995;36:462–7.
- Ben-Menachem T, Decker A, Early DS *et al.* Adverse events of upper GI endoscopy. *Gastrointest Endosc* 2012;76:707–18.
- Barton PM, Moayyedi P, Talley NJ *et al.* Cost effectiveness analysis: applications. *Med Decision Making* 2008;28:33–43.
- National Cancer Institute, Surveillance, Epidemiology, and End Results program. <http://seer.cancer.gov/data/>. Accessed on 24 May 2016.
- Statistics Canada. Table 102-0551. Deaths and mortality rate, by selected grouped causes, age group and sex, Canada, annual (table). CANSIM (database). Date modified: 10 December 2015. Available at: <http://www5.statcan.gc.ca/cansim/a26?lang=eng&tid=1020552>. Accessed on 26 January 2016.
- Vakil N, Talley N, van Zanten SV *et al.* Cost of detecting malignant lesions by endoscopy in 2741 primary care dyspeptic patients without alarm symptoms. *Clin Gastroenterol Hepatol* 2009;7:756–61.
- International Agency for Research on Cancer. <http://gco.iarc.fr/today/home>. Accessed on 12 May 2016.
- Vakil N, Moayyedi P, Fennerty MB *et al.* Limited value of alarm features in the diagnosis of upper gastrointestinal malignancy: systematic review and meta-analysis. *Gastroenterology* 2006;131:390–401.
- Moayyedi P, Talley N, Fennerty MB *et al.* Can the clinical history distinguish between organic and functional dyspepsia? *JAMA* 2006;295:1566–76.
- Collins GS, Altman DG. Identifying patients with undetected gastrooesophageal cancer in primary care: external validation of QCancer<sup>®</sup> (Gastro-Oesophageal). *Eur J Cancer* 2013;49:1040–8.
- Jones R, Latinovic R, Charlton J *et al.* Alarm symptoms in early diagnosis of cancer in primary care" cohort study using General Practice Research Database. *BMJ* 2007;334:1040.
- Stapley S, Peters TJ, Neal RD *et al.* The risk of oesophago-gastric cancer in symptomatic patients in primary care: a large case-control study using electronic records. *Br J Cancer* 2013;108:25–31.
- National Collaborating Centre for Cancer. Suspected Cancer: recognition and referral. NICE guideline June 2015 (NG-12). <http://www.nice.org.uk/guidance/NG12/evidence>. Accessed on 12 May 2016.
- Heaney A, Collins JSA, Watson RGP *et al.* A prospective randomised trial of a "test and treat" policy versus endoscopy based management in young *Helicobacter pylori* positive patients with ulcer-like dyspepsia, referred to a hospital clinic. *Gut* 1999;45:186–90.
- Lassen AT, Pedersen FM, Bytzer P *et al.* *Helicobacter pylori* test-and-eradicate versus prompt endoscopy for management of dyspeptic patients: a randomised trial. *Lancet* 2000;356:455–60.
- McColl KE, Murray LS, Gillen D *et al.* Randomised controlled trial of endoscopy with testing for *Helicobacter pylori* compared with non-invasive *H pylori* testing alone in the management of dyspepsia. *BMJ* 2002;324:999.



41. Arents NLA, Thijs JC, van Zwet AA *et al.* Approach to treatment of dyspepsia in primary care: a randomised trial comparing 'test and treat' with prompt endoscopy. *Arch Intern Med* 2003;163:1606–12.
42. Mahadeva S, Chia YC, Vinothini A *et al.* Cost-effectiveness of and satisfaction with a *Helicobacter pylori* "test and treat" strategy compared with prompt endoscopy in young Asians with dyspepsia. *Gut* 2008;57:1214–20.
43. Duggan AE, Elliott CA, Miller P *et al.* Clinical trial: a randomized trial of early endoscopy, *Helicobacter pylori* testing and empirical therapy for the management of dyspepsia in primary care. *Aliment Pharmacol Ther* 2009;29:55–68.
44. Myres P, Thalanany M, Wilkinson C *et al.* Open Access Endoscopy for *Helicobacter pylori* Positive Patients With Dyspepsia in General Practice, Is It Necessary? University of Wales College of Medicine—Final Study report, 2002.
45. Chiba N, Veldhuyzen van Zanten SJO, Sinclair P *et al.* Treating *Helicobacter pylori* infection in primary care patients with uninvestigated dyspepsia: the Canadian adult dyspepsia empiric treatment—*Helicobacter pylori* positive (CADET-HP) randomised controlled trial. *BMJ* 2002;324:1012–7.
46. Stevens R, Baxter G. Benefit of *Helicobacter pylori* eradication in the treatment of ulcer-like dyspepsia in primary care. *Gastroenterology* 2001;120(5 Suppl 1):A50.
47. Manes G, Mencheise A, de Nucci C *et al.* Empirical prescribing for dyspepsia: randomised controlled trial of test and treat versus omeprazole treatment. *BMJ* 2003;326:1118.
48. Jarbol DE, Kragstrup J, Stovring H *et al.* Proton pump inhibitor or testing for *Helicobacter pylori* as the first step for patients presenting with dyspepsia? A cluster-randomized trial. *Am J Gastroenterol* 2006;101:1200–8.
49. Delaney BC, Qume M, Moayyedi P *et al.* *Helicobacter pylori* test and treat versus proton pump inhibitor in initial management of dyspepsia in primary care: multicentre randomised controlled trial (MRC-CUBE trial). *BMJ* 2008;336:651–4.
50. Ford AC, Moayyedi P, Jarbol DE *et al.* Meta-analysis: *H. pylori* "test and treat" compared with empirical acid suppression for managing dyspepsia? *Aliment Pharmacol Ther* 2008;28:534–44.
51. Ford AC, Forman D, Hunt R *et al.* *Helicobacter pylori* eradication for the prevention of gastric cancer. *Cochrane Database Syst Rev* 2015;7:CD005583.
52. Ford AC, Forman D, Hunt RH *et al.* *Helicobacter pylori* eradication therapy to prevent gastric cancer in healthy asymptomatic infected individuals: systematic review and meta-analysis of randomised controlled trials. *BMJ* 2014;348:g3174.
53. Meineche-Schmidt V, Krag E. Antisecretory therapy in 1017 patients with ulcerlike or reflux-like dyspepsia in general practice. *Eur J General Pract* 1997;3:125–30.
54. Goves J, Oldring JK, Kerr D *et al.* First line treatment with omeprazole provides an effective and superior alternative strategy in the management of dyspepsia compared to antacid/alginate liquid: a multicentre study in general practice. *Aliment Pharmacol Ther* 1998;12:147–57.
55. Rabeneck L, Soucek J, Wristers K *et al.* A double blind, randomized, placebo-controlled trial of proton pump inhibitor therapy in patients with uninvestigated dyspepsia. *Am J Gastroenterol* 2002;97:3045–51.
56. Meineche-Schmidt V. Empiric treatment with high and standard dose of Omeprazole in General Practice: two-week randomised placebo controlled trial and 12 month follow up of healthcare consumption. *Am J Gastroenterol* 2004;99:1050–8.
57. Veldhuyzen van Zanten SJ, Chiba N, Armstrong D *et al.* A randomized trial comparing omeprazole, ranitidine, cispapride, or placebo in *Helicobacter pylori* negative, primary care patients with dyspepsia: the CADET-HN Study. *Am J Gastroenterol* 2005;100:1477–88.
58. Baysal B, Şentürk H, Masri O *et al.* Effect of pantoprazole and *Helicobacter pylori* therapy on uninvestigated dyspeptic patients. *Turk J Gastroenterol* 2015;26:6–14.
59. Jones RH, Baxter G. Lansoprazole 30 mg daily versus ranitidine 150 mg b.d. in the treatment of acid-related dyspepsia in general practice. *Aliment Pharmacol Ther* 1997;11:541–6.
60. Mason I, Millar LJ, Sheikh RR *et al.* The management of acid-related dyspepsia in general practice: a comparison of an omeprazole versus an antacid-alginate/ranitidine management strategy. *Complete Research Group.* *Aliment Pharmacol Ther* 1998;12:263–71.
61. Dewan B, Philipose N. Lafutidine 10 mg versus rabeprazole 20 mg in the treatment of patients with heartburn-dominant uninvestigated dyspepsia: a randomized, multicentric trial. *Gastroenterol Res Pract* 2011;2011:640685.
62. Sakurai K, Nagahara A, Inoue K *et al.* Efficacy of omeprazole, famotidine, mosapride and teprenone in patients with upper gastrointestinal symptoms: an omeprazole-controlled randomized study (J-FOCUS). *BMC Gastroenterol* 2012;12:42.
63. Maity S, Choudhury S, Hazra A *et al.* Randomized controlled trial of effectiveness of lafutidine versus pantoprazole in uninvestigated dyspepsia. *Indian J Pharmacol* 2014;46:498–502.
64. Bytzer P, Hansen JM, Schaffalitzky de Muckadell OB. Empirical H<sub>2</sub>-blocker therapy or prompt endoscopy in management of dyspepsia. *Lancet* 1994;343:811–6.
65. Delaney BC, Wilson S, Roalfe A *et al.* Cost-effectiveness of initial endoscopy for dyspepsia in patients over the age of 50 years: a randomised controlled trial in primary care. *Lancet* 2000;356:1965–9.
66. Lewin-van den Broek NT, Numans ME, Buskens E *et al.* A randomised controlled trial of four management strategies for dyspepsia: relationships between symptom subgroups and strategy outcome. *Br J General Pract* 2001;51:619–24.
67. Kjeldsen HC, Bech M, Christensen B. Cost-effectiveness analysis of two management strategies for dyspepsia. *Int J Technol Assess Health Care* 2007;23:376–84.
68. Moayyedi P, Talley NJ. Gastro-esophageal reflux disease. *Lancet* 2006;367:2086–100.
69. Ford AC, Delaney B, Forman D *et al.* Eradication therapy for peptic ulcer disease in *Helicobacter pylori* positive patients (Cochrane Review). In: *The Cochrane Library*, Issue 1, Wiley: Chichester, UK, 2004.
70. US Food and Drug Administration. <http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm170934.htm>. Accessed on 8 September 2016.
71. Health Canada. <http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2015/43423a-eng.php>. Accessed on 8 September 2016.
72. Ford AC, Luthra P, Tack J *et al.* Efficacy of psychotic drugs in functional dyspepsia: systematic review and meta-analysis. *Gut* 2016;66:411–20.
73. Ford AC, Marwaha A, Lim A *et al.* What is the prevalence of clinically significant endoscopic finding in subjects with dyspepsia? Systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2010;8:830–7.
74. Suzuki H, Moayyedi P. *Helicobacter pylori* infection in functional dyspepsia. *Nat Rev Gastroenterol Hepatol* 2013;10:168–74.
75. Ang TL, Fock KM, Teo EK *et al.* *Helicobacter pylori* eradication versus prokinetics in the treatment of functional dyspepsia: a randomized, double-blind study. *J Gastroenterol* 2006;41:647–53.
76. Blum AL, Talley NJ, O'Morain C *et al.* Lack of effect of treating *Helicobacter pylori* infection in patients with nonulcer dyspepsia. Omeprazole plus Clarithromycin and Amoxicillin Effect One Year after Treatment (OCAY) Study Group. *N Engl J Med* 1998;339:1875–81.
77. Froehlich F, Gonvers J-J, Wietlisbach V *et al.* *Helicobacter pylori* eradication treatment does not benefit patients with non-ulcer dyspepsia. *Am J Gastroenterol* 2001;96:2329–36.
78. Gisbert JP, Cruzado AI, Garcia-Gravalos R *et al.* Lack of benefit of treating *Helicobacter pylori* infection in patients with functional dyspepsia. Randomized one-year follow-up study. *Hepatogastroenterology* 2004;51:303–8.
79. Gonzalez Carro P, Legaz Huidobro ML, Perez Roldan F *et al.* Efficacy of *Helicobacter pylori* eradication in non-ulcer dyspepsia. *Med Clin* 2004;122:87–91.
80. Gwee KA, Teng L, Wong RK *et al.* The response of Asian patients with functional dyspepsia to eradication of *Helicobacter pylori* infection. *Eur J Gastroenterol Hepatol* 2009;21:417–24.
81. Hsu PI, Lai KH, Tseng HH *et al.* Eradication of *Helicobacter pylori* prevents ulcer development in patients with ulcer-like functional dyspepsia. *Aliment Pharmacol Ther* 2001;15:195–201.
82. Koelz HR, Arnold R, Stolte M *et al.* Treatment of *Helicobacter pylori* in functional dyspepsia resistant to conventional management: a double blind randomised trial with a six month follow up. *Gut* 2003;52:40–6.
83. Koskenpato J, Farkkila M, Sipponen P. *Helicobacter pylori* eradication and standardized 3-month omeprazole therapy in functional dyspepsia. *Am J Gastroenterol* 2001;96:2866–72.
84. Lan L, Yu J, Chen YL *et al.* Symptom-based tendencies of *Helicobacter pylori* eradication in patients with functional dyspepsia. *World J Gastroenterol* 2011;17:3242–7.
85. Malfertheiner P, Mossner J, Fischbach W *et al.* *Helicobacter pylori* eradication is beneficial in the treatment of functional dyspepsia. *Aliment Pharmacol Ther* 2003;18:615–25.
86. Martinek J, Spicak J, Benes M *et al.* Effect of eradicating *H. pylori* on the appearance of esophageal reflux disease: randomized double blind study. *Prakt Lek* 2005;85:25.

87. Mazzoleni LE, Sander GB, Ott EA *et al.* Clinical outcomes of eradication of *Helicobacter pylori* in nonulcer dyspepsia in a population with a high prevalence of infection: results of a 12-month randomized, double blind, placebo-controlled study. *Dig Dis Sci* 2006;51:89–98.
88. Mazzoleni LE, Sander GB, Francesconi CF *et al.* *Helicobacter pylori* eradication in functional dyspepsia: HEROES trial. *Arch Intern Med* 2011;171:1929–36.
89. McColl K, Murray L, El-Omar E *et al.* Symptomatic benefit from eradicating *Helicobacter pylori* infection in patients with nonulcer dyspepsia. *N Engl J Med* 1998;339:1869–74.
90. Miwa H, Hirai S, Nagahara A *et al.* Cure of *Helicobacter pylori* infection does not improve symptoms in non-ulcer dyspepsia patients—a double-blind placebo-controlled study. *Aliment Pharmacol Therap* 2000;14:317–24.
91. Ruiz Garcia A, Gordillo Lopez FJ, Hermosa Hernan JC *et al.* Effect of the *Helicobacter pylori* eradication in patients with functional dyspepsia: randomised placebo-controlled trial. *Med Clin* 2005;124:401–5.
92. Sodhi JS, Javid G, Zargar SA *et al.* Prevalence of *Helicobacter pylori* infection and the effect of its eradication on symptoms of functional dyspepsia in Kashmir, India. *J Gastroenterol Hepatol* 2013;28:808–13.
93. Talley NJ, Janssens J, Lauritsen K *et al.* Eradication of *Helicobacter pylori* in functional dyspepsia: randomised double blind placebo controlled trials with 12 months follow up. The Optimal Regimen Cures *Helicobacter* Induced Dyspepsia (ORCHID) Study Group. *Br Med J* 1999;318:833–7.
94. Talley NJ, Vakil N, Ballard ED *et al.* Absence of benefit of eradicating *Helicobacter pylori* in patients with nonulcer dyspepsia. *N Engl J Med* 1999;341:1106–11.
95. Veldhuyzen van Zanten S, Fedorak RN, Lambert J *et al.* Absence of symptomatic benefit of lansoprazole, clarithromycin, and amoxicillin triple therapy in eradication of *Helicobacter pylori* positive, functional (nonulcer) dyspepsia. *Am J Gastroenterol* 2003;98:1963–9.
96. Bruley Des Varannes S, Fléjou JF, Colin R *et al.* There are some benefits for eradicating *Helicobacter pylori* in patients with non-ulcer dyspepsia. *Aliment Pharmacol Ther* 2001;15:1177–85.
97. Moayyedi P, Soo S, Deeks J *et al.* Systematic review and economic evaluation of *Helicobacter pylori* eradication treatment for non-ulcer dyspepsia. *Br Med J* 2000;321:659–64.
98. Moayyedi P. *Helicobacter pylori* eradication for functional dyspepsia: what are we treating? *Arch Intern Med* 2011;171:1936–8.
99. Ishii M, Kusunoki H, Manabe N *et al.* Evaluation of duodenal hypersensitivity induced by duodenal acidification using transnasal endoscopy. *J Gastroenterol Hepatol* 2010;25:913–8.
100. Blum A, Arnold R, Stolte M *et al.* Short course acid suppressive treatment for patients with functional dyspepsia: results depend on *Helicobacter pylori* status. *Gut* 2000;47:473–80.
101. Bolling-Sternevald E, Lauritsen K, Aalykke C *et al.* Effect of profound acid suppression in functional dyspepsia: a double-blind, randomized, placebo-controlled trial. *Scand J Gastroenterol* 2002;37:1395–402.
102. Farup PG, Hovde O, Torp R *et al.* Patients with functional dyspepsia responding to omeprazole have a characteristic gastro-oesophageal reflux pattern. *Scand J Gastroenterol* 1999;34:575–9.
103. Fletcher J, Derakhshan MH, Jones GR *et al.* BMI is superior to symptoms in predicting response to proton pump inhibitor: randomised trial in patients with upper gastrointestinal symptoms and normal endoscopy. *Gut* 2011;60:442–8.
104. Gerson LB, Triadafilopoulos G. A prospective study of oesophageal 24-h ambulatory pH monitoring in patients with functional dyspepsia. *Dig Liver Dis* 2005;37:87–91.
105. Iwakiri R, Tomimaga K, Furuta K *et al.* Randomised clinical trial: rabeprazole improves symptoms in patients with functional dyspepsia in Japan. *Aliment Pharmacol Ther* 2013;38:729–40.
106. Peura DA, Kovacs TO, Metz DC *et al.* Lansoprazole in the treatment of functional dyspepsia: two double-blind, randomized, placebo-controlled trials. *Am J Med* 2004;116:740–8.
107. Suzuki H, Kusunoki H, Kamiya T *et al.* Effect of lansoprazole on the epigastric symptoms of functional dyspepsia (ELF study): a multicentre, prospective, randomized, double-blind, placebo-controlled clinical trial. *United Eur Gastroenterol J* 2013;1:445–52.
108. Talley NJ, Meineche-Schmidt V, Paré P *et al.* Efficacy of omeprazole in functional dyspepsia: double-blind, randomized, placebo-controlled trials (the Bond and Opera studies). *Aliment Pharmacol Ther* 1998;12:1055–65.
109. Talley NJ, Vakil N, Lauritsen K *et al.* Randomized-controlled trial of esomeprazole in functional dyspepsia patients with epigastric pain or burning: does a 1-week trial of acid suppression predict symptom response? *Aliment Pharmacol Ther* 2007;26:673–82.
110. van Rensburg C, Berghöfer P, Enns R *et al.* Efficacy and safety of pantoprazole 20 mg once daily treatment in patients with ulcer-like functional dyspepsia. *Curr Med Res Opin* 2008;24:2009–18.
111. van Zanten SV, Armstrong D, Chiba N *et al.* Esomeprazole 40 mg once a day in patients with functional dyspepsia: the randomized, placebo-controlled "ENTER" trial. *Am J Gastroenterol* 2006;101:2096–106.
112. Wong WM, Wong BCY, Hung WK *et al.* Double blind, randomised, placebo controlled study of four weeks of lansoprazole for the treatment of functional dyspepsia in Chinese patients. *Gut* 2002;51:502–6.
113. Hengels KJ. Therapeutic efficacy of 15 mg lansoprazole mane in 269 patients suffering from non-ulcer dyspepsia (NUD): a multicentre, randomised, double-blind study. *Gut* 1998;43(Suppl 2):A89.
114. Dillon JF, Finch PJ, Baxter G. A comparison of lansoprazole vs. ranitidine in the treatment of functional ulcer-like dyspepsia as defined by Rome II criteria. *Gut* 2004;53(Suppl 6):A285–A286.
115. Hsu Y-C, Liou J-M, Yang T-H *et al.* Proton pump inhibitor versus prokinetic therapy in patients with functional dyspepsia: is a therapeutic response predicted by Rome III subgroups? *J Gastroenterol* 2011;46:183–90.
116. Jian Q, Ding X, Zhang S *et al.* Comparison of mosapride and pantoprazole in treating functional dyspepsia. *Chin J Gastroenterol* 2011;16:547–50.
117. Jung H-K, Lee KJ, Choi M-G *et al.* Efficacy of DA-9701 (Motilitone) in Functional Dyspepsia Compared to Pantoprazole: A Multicenter, Randomized, Double-blind, Non-inferiority Study. *J Neurogastroenterol Motil* 2016;22:254–63.
118. Li Z, Xu G, Du Y *et al.* Low-dose omeprazole in the treatment of functional dyspepsia. *Chin J Gastroenterol* 2003;8:337–9.
119. Moayyedi P, Delaney B, Vakil N *et al.* The efficacy of proton pump inhibitors in non-ulcer dyspepsia: a systematic review and economic analysis. *Gastroenterology* 2004;127:1329–37.
120. Kia L, Kahrilas PJ. Therapy: risk associated with chronic PPI use—signal or noise? *Nat Rev Gastroenterol Hepatol* 2016;13:253–4.
121. Moayyedi P, Leontiadis GI. The risks of PPI therapy. *Nat Rev Gastroenterol Hepatol* 2012;9:132–9.
122. Moayyedi P, Yuan Y, Leontiadis G *et al.* Canadian Association of Gastroenterology position statement: hip fracture and proton pump inhibitor therapy—a 2013 update. *Can J Gastroenterol* 2013;27:593–5.
123. US Food and Drug Administration. <http://www.fda.gov/Drugs/Drug-Safety/ucm290510.htm>. Accessed on 8 September 2016.
124. Ford AC, Quigley EM, Lacy BE *et al.* Effect of antidepressants and psychological therapies, including hypnotherapy, in irritable bowel syndrome: systematic review and meta-analysis. *Am J Gastroenterol* 2014;109:1350–65.
125. Ford AC, Marwaha A, Lim A *et al.* Systematic review and meta-analysis of the prevalence of irritable bowel syndrome in individuals with dyspepsia. *Clin Gastroenterol Hepatol* 2010;8:401–9.
126. Braak B, Klooker TK, Wouters MM *et al.* Randomised clinical trial: the effects of amitriptyline on drinking capacity and symptoms in patients with functional dyspepsia, a double-blind placebo-controlled study. *Aliment Pharmacol Ther* 2011;34:638–48.
127. Wu JC, Cheong PK, Chan Y *et al.* A randomized, double-blind, placebo-controlled trial of low dose imipramine for treatment of refractory functional dyspepsia. *Gastroenterology* 2011;140(Suppl 1):S50.
128. Talley NJ, Locke GR, Saito YA *et al.* Effect of amitriptyline and escitalopram on functional dyspepsia: a multi-center, randomized, controlled study. *Gastroenterology* 2015;149:340–9.e2.
129. Tan VP, Cheung TK, Wong WM *et al.* Treatment of functional dyspepsia with sertraline: a double-blind randomized placebo-controlled pilot study. *World J Gastroenterol* 2012;18:6127–33.
130. Tack J, Masaoka T, Janssen P. Functional dyspepsia. *Curr Opin Gastroenterol* 2011;27:549–57.
131. Lacy BE, Talley NJ, Locke GR *et al.* Review article: current treatment options and management of functional dyspepsia. *Aliment Pharmacol Therap* 2012;36:3–15.
132. Al-Quorain A, Larbi EB, al-Shedoki F. A double-blind, randomized, placebo-controlled trial of cisapride in Saudi Arabs with functional dyspepsia. *Scand J Gastroenterol* 1995;30:531–4.
133. Champion MC, MacCannell KL, Thomson AB *et al.* A double-blind randomized study of cisapride in the treatment of nonulcer dyspepsia. The Canadian Cisapride Nud Study Group. *Can J Gastroenterol* 1997;11:127–34.
134. Chung JM. Cisapride in chronic dyspepsia: results of a double-blind, placebo-controlled trial. *Scand J Gastroenterol Suppl* 1993;195:11–14. Erratum in: *Scand J Gastroenterol Suppl* 1993; 28: 749.
135. Creyten G. Effect of the non-antidopaminergic drug cisapride on postprandial nausea. *Curr Therap Res* 1984;36:1063–70.

136. de Groot GH, de Both PS. Cisapride in functional dyspepsia in general practice. A placebo-controlled, randomized, double-blind study. *Aliment Pharmacol Ther* 1997;11:193-9.
137. De Nutte N, Van Ganse W, Witterhulge M *et al*. Relief of epigastric pain in nonulcer dyspepsia: controlled trial of the promotility drug cisapride. *Clin Ther* 1989;11:62-8.
138. Francois I, De Nutte N. Non-ulcer dyspepsia: effect of the gastrointestinal prokinetic drug cisapride. *Curr Ther Res* 1987;41:891-8.
139. Hallerback BI, Bommelaer G, Bredberg E *et al*. Dose finding study of mosapride in functional dyspepsia: a placebo-controlled, randomized study. *Aliment Pharmacol Ther* 2002;16:959-67.
140. Hannon R. Efficacy of cisapride in patients with non-ulcer dyspepsia. *Curr Ther Res* 1987;42:814-22.
141. Hansen JM, Bytzer P, Schaffalitzky de Muckadell OB. Placebo-controlled trial of cisapride and nizatidine in unselected patients with functional dyspepsia. *Am J Gastroenterol* 1998;93:368-74.
142. Holtmann G, Gschossmann J, Mayr P *et al*. A randomized placebo-controlled trial of simethicone and cisapride for the treatment of patients with functional dyspepsia. *Aliment Pharmacol Ther* 2002;16:1641-8.
143. Holtmann G, Talley NJ, Liebrechts T *et al*. A placebo-controlled trial of itopride in functional dyspepsia. *N Engl J Med* 2006;354:832-40.
144. Kellow JE, Cowan H, Shuter B *et al*. Efficacy of cisapride therapy in functional dyspepsia. *Aliment Pharmacol Ther* 1995;9:153-60.
145. Matsueda K, Hongo M, Tack J *et al*. Clinical trial: dose-dependent therapeutic efficacy of acotiamide hydrochloride (Z-338) in patients with functional dyspepsia—100 mg tid is an optimal dosage. *Neurogastroenterol Motil* 2010;22:618-e173.
146. Matsueda K, Hongo M, Tack J *et al*. A placebo-controlled trial of acotiamide for meal-related symptoms of functional dyspepsia. *Gut* 2012;61:821-8.
147. Miwa H, Nagahara A, Tominaga K *et al*. Efficacy of the 5-HT<sub>1A</sub> agonist tansospirone citrate in improving symptoms of patients with functional dyspepsia: a randomized controlled trial. *Am J Gastroenterol* 2009;104:2779-87.
148. Rösch W. Cisapride in non-ulcer dyspepsia. Results of a placebo-controlled trial. *Scand J Gastroenterol* 1987;22:161-4.
149. Talley NJ, Verlinden M, Snape W *et al*. Failure of a motilin receptor agonist (ABT-229) to relieve the symptoms of functional dyspepsia in patients with and without delayed gastric emptying: a randomized double-blind placebo-controlled trial. *Aliment Pharmacol Ther* 2000;14:1653-61.
150. Talley NJ, Van Zanten SV, Saez LR *et al*. A dose-ranging, placebo-controlled, randomized trial of alosetron in patients with functional dyspepsia. *Aliment Pharmacol Ther* 2001;15:525-37.
151. Talley NJ, Tack J, Ptak T *et al*. Itopride in functional dyspepsia: results of two phase III multicentre, randomised, double-blind, placebo-controlled trials. *Gut* 2008;57:740-6.
152. Vakil N, Laine L, Talley NJ *et al*. Tegaserod treatment for dysmotility-like functional dyspepsia: results of two randomized, controlled trials. *Am J Gastroenterol* 2008;103:1906-19.
153. Wood SF, Penney SC, Cochran KM. Cisapride in functional dyspepsia: a double-blind, placebo-controlled randomized trial in general practice patients. *Scand J Gastroenterol Suppl* 1993;195:5-10.
154. Yeoh KG, Kang JY, Tay HH *et al*. Effect of cisapride on functional dyspepsia in patients with and without histological gastritis: a double-blind placebo-controlled trial. *J Gastroenterol Hepatol* 1997;12:13-8.
155. Bekhti A, Rutgeerts L. Domperidone in the treatment of functional dyspepsia in patients with delayed gastric emptying. *Postgrad Med J* 1979;55(Suppl 1):30-2.
156. Chey WY, You CH, Ange DA. Open and double blind clinical trials of domperidone in patients with unexplained nausea, vomiting, abdominal bloating and early satiety. *Gastroenterology* 1982;82(Suppl 1):1033.
157. Davis RH, Clench MH, Mathias JR. Effects of domperidone in patients with chronic unexplained upper gastrointestinal symptoms: a double-blind placebo-controlled study. *Dig Dis Sci* 1988;33:1505-11.
158. Haarmann K, Lebkuchner F, Widmann A *et al*. A double-blind study of domperidone in the symptomatic treatment of chronic post-prandial upper gastrointestinal distress. *Postgrad Med J* 1979;55(suppl 1):24-7.
159. Van de Mierop L, Rutgeerts L, Van den Langenbergh B *et al*. Oral domperidone in chronic postprandial dyspepsia. *Digestion* 1979;19:244-50.
160. Van Ganse W, Van Damme L, Van de Mierop L *et al*. Chronic dyspepsia: double-blind treatment with domperidone (R 33 812) or a placebo. A multicentre therapeutic evaluation. *Curr Therap Res* 1978;23:695-702.
161. Van Outryve M, Lauwers W, Verbeke S. Domperidone for the symptomatic treatment of chronic post-prandial nausea and vomiting. *Postgrad Med J* 1979;55(suppl 1):33-5.
162. Soo S, Forman D, Delaney B *et al*. A systematic review of psychological therapies for nonulcer dyspepsia. *Am J Gastroenterol* 2004;99:1817-22.
163. Bates S, Sjoden P-O, Nyren O. Behavioural treatment of non-ulcer dyspepsia. *Scand J Behav Ther* 1988;17:155-65.
164. Calvert EL, Houghton LA, Cooper P *et al*. Long-term improvement in functional dyspepsia using hypnotherapy. *Gastroenterology* 2002;123:1778-85.
165. Cao J, Ren X, Zhu G. Significance of double steps reattribution integrative model for patients with functional dyspepsia (FD) (Abstract). *Gastroenterology* 2013;144(suppl 1):S205-S206.
166. Cheng C, Yang F-C, Jun S *et al*. Flexible coping psychotherapy for functional dyspeptic patients: a randomized, controlled trial. *Psychosom Med* 2007;69:81-8.
167. Dehghanizade Z, Zargar Y, Honarmand MM *et al*. The effectiveness of cognitive behavior stress management on functional dyspepsia symptoms. *J Adv Med Educ Prof* 2015;3:45-9.
168. Faramarzi M, Azadfallah P, Book HE *et al*. A randomized controlled trial of brief psychoanalytic psychotherapy in patients with functional dyspepsia. *Asian J Psych* 2013;6:228-34.
169. Haag S, Senf W, Tagay S *et al*. Is there a benefit from intensified medical and psychological interventions in patients with functional dyspepsia not responding to conventional therapy? *Aliment Pharmacol Ther* 2007;25:973-86.
170. Hamilton J, Guthrie E, Creed F *et al*. A randomized controlled trial of psychotherapy in patients with chronic functional dyspepsia. *Gastroenterology* 2000;119:661-9.
171. Haug TT, Wilhelmssen I, Svebak S *et al*. Psychotherapy in functional dyspepsia. *J Psychosom Res* 1994;38:735-44.
172. Jiang H, Jiang Y, Zhang S. The effect of psychotherapy intervention on pharmacotherapy of patients with functional dyspepsia. *Pharm Care Res* 2008;8:52-4.
173. Liu XH. Clinical effects of behavioral interventions in elderly patients with functional dyspepsia. *World Chin J Digestol* 2015;23:3940-4.
174. Orive M, Barrio I, Orive VM *et al*. A randomized controlled trial of a 10 week group psychotherapeutic treatment added to standard medical treatment in patients with functional dyspepsia. *J Psychosom Res* 2015;78:563-8.
175. Koloski NA, Talley NJ, Huskic SS *et al*. Predictors of conventional and alternative health care seeking for irritable bowel syndrome and functional dyspepsia. *Aliment Pharmacol Ther* 2003;17:841-51.
176. Stake-Nilsson K, Soderlund M, Hultcrantz R *et al*. A qualitative study of complementary and alternative medicine use in persons with uninvestigated dyspepsia. *Gastroenterol Nurs* 2008;32:107-14.
177. von Arnim U, Peitz U, Vinson B *et al*. STW 5, a phytopharmakon for patients with functional dyspepsia: results of a multicenter, placebo-controlled double-blind study. *Am J Gastroenterol* 2007;102:1268-75.
178. Wang C, Zhu M, Xia W *et al*. Meta-analysis of traditional Chinese medicine in treating functional dyspepsia of liver-stomach disharmony syndrome. *J Tradit Chin Med* 2012;32:515-22.
179. Lan L, Zeng F, Liu GJ *et al*. Acupuncture for functional dyspepsia. *Cochrane Database System Rev* 2014, Issue 10. Art. No.: CD008487 10.1002/14651858.CD008487.pub2.
180. Tack J, Bisschops R, Sarnelli G. Pathophysiology and treatment of functional dyspepsia. *Gastroenterology* 2004;127:1239-55.
181. Lacy BE, Cash BD. A 32-year-old woman with chronic abdominal pain. *JAMA* 2008;299:555-65.
182. Lacy BE. Functional dyspepsia and gastroparesis: One disease or two? *Am J Gastroenterol* 2012;107:1615-20.
183. Ang D. Measurement of gastric accommodation: a reappraisal of conventional and emerging modalities. *Neurogastroenterol Motil* 2011;23:287-91.
184. Talley NJ, Walker MM, Aro P *et al*. Non-ulcer dyspepsia and duodenal eosinophilia: an adult endoscopic population-based case-control study. *Clin Gastroenterol Hepatol* 2007;5:1175-83.
185. van Lelyveld N, Schipper M, Samsom M. Lack of relationship between chronic upper abdominal symptoms and gastric function in functional dyspepsia. *Dig Dis Sci* 2008;53:1223-30.
186. Cassilly DW, Wang YR, Friedenberk FK *et al*. Symptoms of gastroparesis: use of the gastroparesis cardinal symptom index in symptomatic patients referred for gastric emptying scintigraphy. *Digestion* 2008;78:144-51.
187. Camilleri M, Parkman HP, Shafi MA *et al*. Clinical guideline: management of gastroparesis. *Am J Gastroenterol* 2013;108:18-37.
188. Stanghellini V, Tosetti C, Paternico A *et al*. Risk indicators of delayed gastric emptying of solids in patients with functional dyspepsia. *Gastroenterology* 1996;110:1036-42.
189. Sarnelli G, Caenepeel P, Geypens B *et al*. Symptoms associated with impaired gastric emptying of solids and liquids in functional dyspepsia. *Am J Gastroenterol* 2003;98:783-8.



**APPENDIX 1**  
**SEARCH STRATEGIES USED FOR THE DYSPESIA GUIDELINE**

Topic	Medline (Database: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>	Embase <1974 to present
Psychological therapy, from 2005 to 12 May 2016, Multi-file search, n=745	<ol style="list-style-type: none"> <li>1 exp Dyspepsia/ (7,888)</li> <li>2 eructation/ (328)</li> <li>3 flatulence/ (1,301)</li> <li>4 (dyspep* or "NUD" or "FD"),mp. (20,895)</li> <li>5 (indigestion or indigestive).tw,kw. (799)</li> <li>6 1 or 2 or 3 or 4 or 5 (22,982)</li> <li>7 exp Psychotherapy/(167,526)</li> <li>8 psychotherap*.af. (103,197)</li> <li>9 (animal assisted or aromatherapy or art or behavior or behaviour or color or colour or dance or feedback or music or narrative or person-centered or play or psychoanalytic* or psycholog* or therapy* or treat* or manag* or strategy*).tw,kw. (67,724)</li> <li>10 ((horticultural or socioenvironmental or social environment or socio* environment or logotherapy* or reality or gestalt) adj5 (therap* or treat* or manag* or strategy*).tw,kw. (2,178)</li> <li>11 (autogenic training or (relaxation adj2 progressive) or bibliotherapy* or hypnosis or hypnoses or hypnotherap* or hypnotism or mesmerism or abreaction or catharsis).tw,kw. (9,967)</li> <li>12 or/7-11 (254,628)</li> <li>13 6 and 12 (253)</li> <li>14 randomized controlled trial.pt. (416,221)</li> <li>15 controlled clinical trial.pt. (90,701)</li> <li>16 random*.mp. (1,046,809)</li> <li>17 placebo.ab. (171,882)</li> <li>18 trial.ab. (364,897)</li> <li>19 groups.ab. (1,579,013)</li> <li>20 or/14-19 (2,535,619)</li> <li>21 13 and 20 (78)</li> <li>22 limit 21 to yr="2005-Current" (42)</li> </ol>	<ol style="list-style-type: none"> <li>1 exp Dyspepsia/ (28,265)</li> <li>2 eructation/ (983)</li> <li>3 flatulence/ (9,815)</li> <li>4 (dyspep* or "NUD" or "FD"),mp. (42,121)</li> <li>5 (indigestion or indigestive).tw,kw. (1,203)</li> <li>6 1 or 2 or 3 or 4 or 5 (52,030)</li> <li>7 exp Psychotherapy/(209,526)</li> <li>8 psychotherap*.af. (139,519)</li> <li>9 (animal assisted or aromatherapy or art or behavior or behaviour or color or colour or dance or feedback or music or narrative or person-centered or play or psychoanalytic* or psycholog* or therap* or treat* or manag* or strategy*).tw,kw. (95,906)</li> <li>10 ((horticultural or socioenvironmental or social environment or socio* environment or logotherapy* or reality or gestalt) adj5 (therap* or treat* or manag* or strategy*).tw,kw. (3,158)</li> <li>11 (autogenic training or (relaxation adj2 progressive) or bibliotherapy* or hypnosis or hypnoses or hypnotherap* or hypnotism or mesmerism or abreaction or catharsis).tw,kw. (12,483)</li> <li>12 or/7-11 (332,259)</li> <li>13 6 and 12 (1,203)</li> <li>14 random*.mp. (1,250,429)</li> <li>15 clinical trial:mp. (1,213,928)</li> <li>16 exp health care quality/ (2,307,441)</li> <li>17 double-blind:mp. or placebo.tw. or blind:tw. (462,289)</li> <li>18 or/14-17 (4,013,838)</li> <li>19 13 and 18 (766)</li> <li>20 limit 19 to yr="2005-Current" (602)</li> </ol>
Prokinetics and FD from 2010 to 12 April 2016, Multi-file search, n=1,026	<ol style="list-style-type: none"> <li>1 exp Dyspepsia/7,859</li> <li>2 (dyspep* or "NUD" or "FD").tw,kw. 18,461</li> <li>3 (indigestion or indigestive).tw. 783</li> <li>4 or/1-3 20,884</li> <li>5 (prokinetic* or gastroprokinetic* or gastrokinetic* or gastro-kinetic*).tw,kw. 2,687</li> <li>6 (antiemetic* or anti-emetic).tw,kw. 7,327</li> <li>7 exp Benzamides/46,246</li> <li>8 (Benzoic Acid Amide or Amides or Phenyl Carboxamide or Benzamide* or Benzoylamide or benzoates).tw,kw. 13,430</li> <li>9 (Phenylcarboxamide or Phenylcarboxamide or Benzenecarboxamide or Amid kyseliny/benzoove).tw,kw. 12</li> <li>10 exp Domperidone/1,623</li> <li>11 (domperidon* or domidon or Domperi or Domstal or evoxin or gastrocure or motilium or motilium).tw,kw. 2,103</li> <li>12 (motis or nauzelin or Motinorm Costi or Nomit or Brullium or Molax).tw,kw. 4</li> <li>13 exp Antiemetics/133,454</li> <li>14 exp Metoclopramide/4,630</li> <li>15 (Metoclopramide or cerucal or clopra or gastrese or gastrobid or gastroflux or gastromax or maxolon).tw,kw. 5,414</li> <li>16 (metaclopramide or metozolv or metramid or migravess or mygdalon or oclamide or parmid).tw,kw. 45</li> <li>17 (primperan or reglan or reliveran or rimetin or Degan or Maxeran or Pylomid or Pramim).tw,kw. 115</li> <li>18 exp Cisapride/1,444</li> <li>19 (Cisapride or alimix or Prepulsid or Propulsid).tw,kw. 1,675</li> <li>20 exp Cholinesterase Inhibitors/44,836</li> </ol>	<ol style="list-style-type: none"> <li>1 exp dyspepsia/28,132</li> <li>2 (dyspep* or "NUD" or "FD").tw,kw. 26,029</li> <li>3 (indigestion or indigestive).tw. 1,188</li> <li>4 or/1-3 42,564</li> <li>5 (prokinetic* or gastroprokinetic* or gastrokinetic* or gastro-kinetic*).tw,kw. 4,035</li> <li>6 (antiemetic* or anti-emetic).tw,kw. 10,216</li> <li>7 exp benzamide derivative/54,971</li> <li>8 (Benzoic Acid Amide or Amides or Phenyl Carboxamide or Benzamide* or Benzoylamide or benzoates).tw,kw. 16,902</li> <li>9 (Phenylcarboxamide or Phenylcarboxamide or Benzenecarboxamide or Amid kyseliny benzoove).tw,kw. 13</li> <li>10 exp domperidone/7,795</li> <li>11 (domperidon* or domidon or Domperi or Domstal or evoxin or gastrocure or motilium or motilium).tw,kw. 3,417</li> <li>12 (motis or nauzelin or Motinorm Costi or Nomit or Brullium or Molax).tw,kw. 16</li> <li>13 exp antiemetic agent/168,619</li> <li>14 exp metoclopramide/22,515</li> <li>15 (Metoclopramide or cerucal or clopra or gastrese or gastrobid or gastroflux or gastromax or maxolon).tw,kw. 7,192</li> <li>16 (metaclopramide or metozolv or metramid or migravess or mygdalon or oclamide or parmid).tw,kw. 114</li> <li>17 (primperan or reglan or reliveran or rimetin or Degan or Maxeran or Pylomid or Pramim).tw,kw. 1,692</li> <li>18 exp cisapride/7,296</li> <li>19 (Cisapride or alimix or Prepulsid or Propulsid).tw,kw. 2,729</li> <li>20 exp cholinesterase inhibitor/77,946</li> </ol>

Appendix Table 1. continued on following page

Topic	Medline (Database: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>	Embase <1974 to present
<p>21 (ltopride or ganaton).tw,kw. 102</p> <p>22 Mosapride.tw,kw. 262</p> <p>23 exp Erythromycin/22,427</p> <p>24 (erythromycin or aknemycin or emcin or engel or emycin or eryderm or erygel or erymax).tw,kw. 18,745</p> <p>25 (erymin or eryped or gallimycin or ilosone or ilotycin or lauromicina or maracyn).tw,kw. 60</p> <p>26 (monomycin or ornacyn or retcin or rommix or romycin or roymicin or staticin or stemycin or therymcyin or tiloyth or wyamycin).tw,kw. 275</p> <p>27 (monomycin or ornacyn or retcin or rommix or romycin or roymicin or staticin or stemycin or therymcyin or tiloyth or wyamycin).tw,kw. 271</p> <p>28 (Motilin adj3 (receptor* or agonist*)).tw,kw. 369</p> <p>29 ((5HT3 or 5HT 3 or 5-HT3) adj3 antagonist*).tw,kw. 3,638</p> <p>30 ((5HT or 5-HT or 5-hydroxytryptamine*) adj3 (agonist* or antagonist*)).tw,kw. 8,795</p> <p>31 ((5-HT1A or 5HT1A or 5-HT 1A or 5HT 1A) adj3 agonist*).tw,kw. 4,069</p> <p>31 exp Serotonin Antagonists/47,240</p> <p>32 exp Serotonin 5-HT3 Receptor Antagonists/612</p> <p>33 exp Serotonin 5-HT4 Receptor Agonists/224</p> <p>34 exp Serotonin 5-HT1 Receptor Agonists/2,887</p> <p>35 (serotonin adj3 receptor adj3 (agonist* or antagonist* or block*)).tw,kw. 2,068</p> <p>36 (tegaserod or Zelnorm or Zelmec).tw,kw. 388</p> <p>37 AB T-229.tw,kw. 22</p> <p>38 (Tandospirone or Sediel or metanopirone or buspirone).tw,kw. 2,603</p> <p>39 (alosetron or Lotronex).tw,kw. 245</p> <p>40 (Acotiamide or YM-443 or Z-338D).tw,kw. 40</p> <p>41 (acetylcholinesterase inhibitor* or cholinesterase Inhibitor* or anti-cholinesterase* or anticholinesterase*).tw,kw. 10,393</p> <p>42 ((5HT-4 or 5HT4 or 5-HT 4 or 5-HT4) adj3 agonist*).tw,kw. 740</p> <p>43 or/5-42 3,16,333</p> <p>44 4 and 43 1,331</p> <p>45 randomized controlled trial.pt. 412,566</p> <p>46 controlled clinical trial.pt. 90,495</p> <p>47 random*.mp. 1,019,981</p> <p>48 placebo.ab. 168,576</p> <p>49 drug therapy.fs. 1,841,827</p> <p>50 trial.ab. 354,331</p> <p>51 groups.ab. 1,539,040</p> <p>52 or/45-51 3,918,006</p> <p>53 exp animals/ not humans.sh. 4,221,321</p> <p>54 52 not 53 3,364,132</p> <p>55 44 and 54 1,058</p> <p>56 limit 55 to yr=2010 -Current* 221</p>	<p>21 (ltopride or ganaton).tw,kw. 226</p> <p>22 exp mosapride/380</p> <p>23 Mosapride.tw,kw. 469</p> <p>24 exp erythromycin/66,403</p> <p>25 (erythromycin or aknemycin or emcin or engel or emycin or eryderm or erygel or erymax).tw,kw. 22,087</p> <p>26 (erymin or eryped or gallimycin or ilosone or ilotycin or lauromicina or maracyn).tw,kw. 275</p> <p>27 (monomycin or ornacyn or retcin or rommix or romycin or roymicin or staticin or stemycin or therymcyin or tiloyth or wyamycin).tw,kw. 271</p> <p>28 exp motilin receptor agonist/69,135</p> <p>29 (Motilin adj3 (receptor* or agonist*)).tw,kw. 458</p> <p>30 ((5HT3 or 5HT 3 or 5-HT3) adj3 antagonist*).tw,kw. 4,824</p> <p>31 ((5HT or 5-HT or 5-hydroxytryptamine*) adj3 (agonist* or antagonist*)).tw,kw. 9,448</p> <p>32 ((5-HT1A or 5HT1A or 5-HT 1A or 5HT 1A) adj3 agonist*).tw,kw. 4,827</p> <p>33 exp serotonin antagonists/120,230</p> <p>34 exp serotonin 3 antagonists/3,440</p> <p>35 exp serotonin 4 agonist/802</p> <p>36 exp serotonin 1 agonist/610</p> <p>37 (serotonin adj3 receptor adj3 (agonist* or antagonist* or block*)).tw,kw. 2,790</p> <p>38 exp tegaserod/ 1,705</p> <p>39 (tegaserod or Zelnorm or Zelmec).tw,kw. 737</p> <p>40 ABT-229.tw,kw. 98</p> <p>41 exp tandospirone/519</p> <p>42 (Tandospirone or Sediel or metanopirone or buspirone).tw,kw. 3,272</p> <p>43 exp alosetron/1,233</p> <p>44 (alosetron or Lotronex).tw,kw. 541</p> <p>45 exp acotiamide/105</p> <p>46 (Acotiamide or YM-443 or Z-338D).tw,kw. 77</p> <p>47 (acetylcholinesterase inhibitor* or cholinesterase Inhibitor* or anti-cholinesterase* or anticholinesterase*).tw,kw. 13,960</p> <p>48 ((5HT-4 or 5HT4 or 5-HT 4 or 5-HT4) adj3 agonist*).tw,kw. 1,013</p> <p>49 or/5-48 452,852</p> <p>50 4 and 49 3,919</p> <p>51 random*.mp. 1,239,350</p> <p>52 placebo.mp. 372,038</p> <p>53 clinical trial:.mp. 1,207,584</p> <p>54 double-blind:.mp. or blind:.tw. 354,000</p> <p>55 or/51-54 2,210,439</p> <p>56 exp animal/ not human/4,594,892</p> <p>57 55 not 56 2,042,185</p> <p>58 50 and 57 2,204</p> <p>59 remove duplicates from 58 2,189</p> <p>60 limit 59 to yr=2010 -Current* 639</p> <p>1 clinical trial/ or (clin\$ adj2 (trial\$ or stud\$)).tw.</p> <p>2 exp Randomized controlled trial/</p> <p>3 exp Randomization/</p> <p>4 Single-Blind Method/</p> <p>5 Double-Blind Method/</p> <p>6 Cross-Over Studies/ or (crossover\$ or cross-over\$).tw.</p> <p>7 exp Random Allocation/</p> <p>8 RCT.tw.</p> <p>9 ((single or double or treble or triple) adj3 (blind\$ or mask\$)).tw.</p>	<p>HP eradication and HP from 2006 to 4 April 2016. Multi-file search, n=1,170</p> <p>1 randomized controlled trial.pt. (338,380)</p> <p>2 controlled clinical trial.pt. (85,027)</p> <p>3 random*.mp. (793,630)</p> <p>4 placebo.ab. (139,962)</p> <p>5 drug therapy.fs. (1,570,375)</p> <p>6 trial.ab. (263,685)</p> <p>7 groups.ab. (1,213,517)</p> <p>8 1 or 2 or 3 or 4 or 5 or 6 or 7 (3,196,892)</p> <p>9 exp animals/ not exp humans/(3,749,652)</p>

Appendix Table 1 continued on following page



Topic	Medline (Database: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>	Embase <1974 to present
<p>PPI and FD from 2002 to 25 Feb 2016, Multi-file search, n=2,670 search in 11 April 2013, n=527 update search in 2016</p>	<p>10.8 not.9 (2,726,261)  11 exp Dyspepsia/ (6,867)  12 eructation/ (276)  13 flatulence/ (1,134)  14 (dyspep\$ or NUD or FD).mp. (17,100)  15 (indigestion or indigestive).tw. (626)  16 11 or 12 or 13 or 14 or 15 (18,878)  17 exp helicobacter/(27,791)  18 exp helicobacter infections/(23,015)  19 exp <i>Helicobacter pylori</i>/(26,780)  20 (helicobacter or pylori or pyloridis or HP or Campylobacter).mp. (57,996)  21 17 or 18 or 19 or 20 (57,996)  22 16 and 21 (3,975)  23 10 and 22 (2,030)  24 limit 23 to yr=2006 -Current* (500)</p>	<p>10 comparative study/  11 controlled study/  12 Prospective study/  13 evaluation studies/  14 random\$.mp.  15 placebo/ or placebo:.mp.  16 (control\$ or prospective\$ or volunteer\$).tw.  17 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 14 or 16  18 exp animal/not exp human/  19 17 not 18  20 exp dyspepsia/  21 eructation/  22 flatulence/  23 (dyspepsia or dyspeptic or NUD or FD).mp.  24 (indigestion or indigestive).tw.  25 20 or 21 or 22 or 23 or 24  26 exp <i>Helicobacter</i>/  27 exp <i>Helicobacter pylori</i>/  28 exp <i>Helicobacter</i> infection/  29 (helicobacter or pylori or pyloridis or HP or Campylobacter).mp.  30 26 or 27 or 28 or 29  31 25 and 30  32 19 and 31 (3,551)  33 limit 32 to yr=2006 -Current* (1,237)</p>
	<p>1. exp dyspepsia/  2. (Dyspepsia or dyspeptic or NUD or FD).mp.  3. (indigestion or indigestive).tw.  4. or/1-3  5. exp Proton Pump Inhibitors/  6. ((proton adj2 pump adj2 inhibitor\$) or PPI or PPIs).tw.  7. Esomeprazole Sodium/  8. (Esomeprazole or Nexium or Esotrex or Alenia or Escz or Esofag or Nexiam).tw.  9. Omeprazole/  10. (omeprazole or lasec or nexium or prilosec or rapinex or zegerid or omeprazole or Omez).tw.  11. (pantoprazole or protonix or protonix or Pantotab or Pantopan or Pantozol or Pantoloc or Pantodac or Zurcal or Zentro).tw.  12. (rabeprazole or aciphex or dexabeprazole or pariet or Zechin or Rabeacid or Nzole-D or Rabeloc).tw.  13. (Dexlansoprazole or Kapidex or Dexilant).tw.  14. (lansoprazole or lanzoprazole or agopton or bimalite or Inhibitol or Levant or Lupizole or lanzor or monolithum or ogastro or opiren or prevacid or ulpax or zoton).tw.  15. or/5-14  16. 4 and 15  17. randomized controlled trial.pt.  18. controlled clinical trial.pt.  19. randomized.ab.  20. placebo.ab.  21. drug therapy.fs.  22. randomly.ab.  23. trial.ab.  24. groups.ab.  25. or/17-24  26. 16 and 25  27. exp animals/ not humans.sh.  28. 26 not.27</p>	<p>1. exp dyspepsia/  2. (Dyspepsia or dyspeptic or NUD or FD).mp.  3. (indigestion or indigestive).tw.  4. or/1-3  5. exp proton pump inhibitor/  6. ((proton adj2 pump adj2 inhibitor\$) or PPI or PPIs).tw.  7. esomeprazole/  8. (Esomeprazole or Nexium or Esotrex or Alenia or Escz or Esofag or Nexiam).tw.  9. omeprazole/  10. (omeprazole or lasec or nexium or prilosec or rapinex or zegerid or lomec or acid or Lomac or Omepral or Omez).tw.  11. pantoprazole/  12. (pantoprazole or protonix or protonix or Pantotab or Pantopan or Pantozol or Pantoloc or Astropan or Controloc or Pantecta or Inipomp or Somac or Pantodac or Zurcal or Zentro).tw.  13. rabeprazole/  14. (rabeprazole or aciphex or dexabeprazole or pariet or Zechin or Rabeacid or Nzole-D or Rabeloc).tw.  15. lansoprazole/  16. (lansoprazole or lanzoprazole or agopton or bimalite or Inhibitol or Levant or Lupizole or lanzor or monolithum or ogastro or opiren or prevacid or prezal or pro ulco or promeco or takepron or ulpax or zoton).tw.  17. (Dexlansoprazole or Kapidex or Dexilant).tw.  18. or/5-17  19. 4 and 18  20. random.:tw. or placebo:.mp. or double-blind.:tw.  21. 19 and 20</p>

Topic	Medline (Database: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>	Embase <1974 to present
Initial management strategies for undiagnostic dyspepsia from 2004 to February 2016 Multi-file search, n=1,989 in 06 August 2014, update search n=414 in 09 February 2016	<ol style="list-style-type: none"> <li>1 exp dyspepsia/ (7,282)</li> <li>2 (dyspep* or FD or NUD).ti,ab,kw. (10,750)</li> <li>3 1 or 2 (12,551)</li> <li>4 exp Proton Pump Inhibitors/ (14,111)</li> <li>5 exp omeprazole/ (8,570)</li> <li>6 exp esomeprazole/(691)</li> <li>7 exp lansoprazole/(1,848)</li> <li>8 exp rabeprazole/(795)</li> <li>9 (proton pump inhibitor* or PPI or PPIs or omeprazole or esomeprazole or lansoprazole or pantoprazole or rabeprazole).ti,ab,kw. (22,117)</li> <li>10 or/4-9 (25,881)</li> <li>11 exp Histamine H<sub>2</sub> Antagonists/(18,410)</li> <li>12 exp ranitidine/(4,990)</li> <li>13 exp cimetidine/(9,164)</li> <li>14 exp famotidine/(1,480)</li> <li>15 exp nizatidine/(300)</li> <li>16 ((histamine H<sub>2</sub> ad5 antagonist* or H<sub>2</sub>-receptor antagonist* or H<sub>2</sub>RA or H<sub>2</sub>RAs or H<sub>2</sub>RA or H<sub>2</sub> RAs or cimetidine or ranitidine or famotidine or nizatidine or roxatidine).ti,ab,kw. (18,135)</li> <li>17 or/11-16 (23,248)</li> <li>18 exp Helicobacter/ or exp <i>Helicobacter pylori</i> or exp Helicobacter infection/ (31,400)</li> <li>19 (helicobacter or pylori or pyloridis or *HP* or Campylobacter).ti,ab,kw. (59,887)</li> <li>20 18 or 19 (62,395)</li> <li>21 (test* adj3 (treat or manage* or therap*))ti,ab,kw. (10,129)</li> <li>22 20 and 21 (369)</li> <li>23 exp Endoscopy/(261,964)</li> <li>24 (endoscop* or Gastroscop* or Duodenoscop*).ti,ab,kw. (59,007)</li> <li>25 23 or 24 (286,034)</li> <li>26 (initial adj3 (investigat* or manage* or procedure or strateg*))ti,ab,kw. (9,656)</li> <li>27 (empirical adj3 treat* or therap* or manage* or strateg*).ti,ab,kw. (5,343)</li> <li>28 10 or 17 or 22 or 25 or 26 or 27 (340,111)</li> <li>29 3 and 28 (4,280)</li> <li>30 randomized controlled trial.pt. (379,756)</li> <li>31 controlled clinical trial.pt. (889,20)</li> <li>32 random\$.mp. (913,711)</li> <li>33 placebo.ab. (156,611)</li> <li>34 drug therapy.fs. (1,719,987)</li> <li>35 trial.ab. (312,630)</li> <li>36 groups.ab. (1,379,836)</li> <li>37 or/30-36 (3,579,084)</li> <li>38 29 and 37 (2,297)</li> <li>39 exp animals/not humans/(3,972,902)</li> <li>40 38 not 39 (2,292)</li> <li>41 limit 40 to yr=2004 -Current* (955)</li> </ol>	<ol style="list-style-type: none"> <li>1 exp dyspepsia/ (25,632)</li> <li>2 (dyspep* or FD or NUD).ti,ab,kw. (14,899)</li> <li>3 1 or 2 (29,332)</li> <li>4 exp proton pump inhibitor/ (52,191)</li> <li>5 exp omeprazole/ (26,121)</li> <li>6 exp esomeprazole/(5,198)</li> <li>7 exp lansoprazole/(8,781)</li> <li>8 exp pantoprazole/(6,458)</li> <li>9 exp rabeprazole/(3,819)</li> <li>10 (proton pump inhibitor* or PPI or PPIs or omeprazole or esomeprazole or lansoprazole or rabeprazole).ti,ab,kw. (31,909)</li> <li>11 or/4-10 (62,185)</li> <li>12 exp histamine H<sub>2</sub>-receptor antagonist/ (61,484)</li> <li>13 exp ranitidine/(21,483)</li> <li>14 exp cimetidine/(30,685)</li> <li>15 exp famotidine/(7,264)</li> <li>16 exp nizatidine/(1,928)</li> <li>17 ((histamine H<sub>2</sub> ad5 antagonist* or H<sub>2</sub>-receptor antagonist* or H<sub>2</sub>RA or H<sub>2</sub>RAs or H<sub>2</sub>-RA or H<sub>2</sub> RAs or cimetidine or ranitidine or famotidine or nizatidine).ti,ab,kw. (23,645)</li> <li>18 or/12-17 (63,515)</li> <li>19 exp Helicobacter/ or exp <i>Helicobacter pylori</i> or exp Helicobacter infection/ (50,719)</li> <li>20 (helicobacter or pylori or pyloridis or *HP* or Campylobacter).ti,ab,kw. (74,711)</li> <li>21 (test* adj3 (treat or manage* or therap*))ti,ab,kw. (13,763)</li> <li>22 (19 or 20) and 21 (471)</li> <li>23 exp endoscopy/ (413,319)</li> <li>24 (endoscop* or Gastroscop* or Duodenoscop*).ti,ab,kw. (88,994)</li> <li>25 23 or 24 (436,324)</li> <li>26 (initial adj3 (investigat* or manage* or procedure or strateg*))ti,ab,kw. (12,734)</li> <li>27 (empirical adj3 treat* or therap* or manage* or strateg*).ti,ab,kw. (7,204)</li> <li>28 11 or 18 or 22 or 25 or 26 or 27 (550,017)</li> <li>29 3 and 28 (9,263)</li> <li>30 random\$.mp. (1,036,938)</li> <li>31 double-blind:.mp. or placebo:.tw. or blind:.tw. (399,530)</li> <li>32 30 or 31 (1,218,944)</li> <li>33 29 and 32 (1,833)</li> <li>34 exp animal/ not human/ (4,408,333)</li> <li>35 33 not 34 (1,831)</li> <li>36 limit 35 to yr=2004 -Current* (1,048)</li> </ol>

APPENDIX 2

Forest plots of meta-analyses that support the dyspepsia guideline.

Figure 1. Forest plot of randomized controlled trials comparing *H. pylori* test and treat with early endoscopy with continued dyspepsia as the outcome.

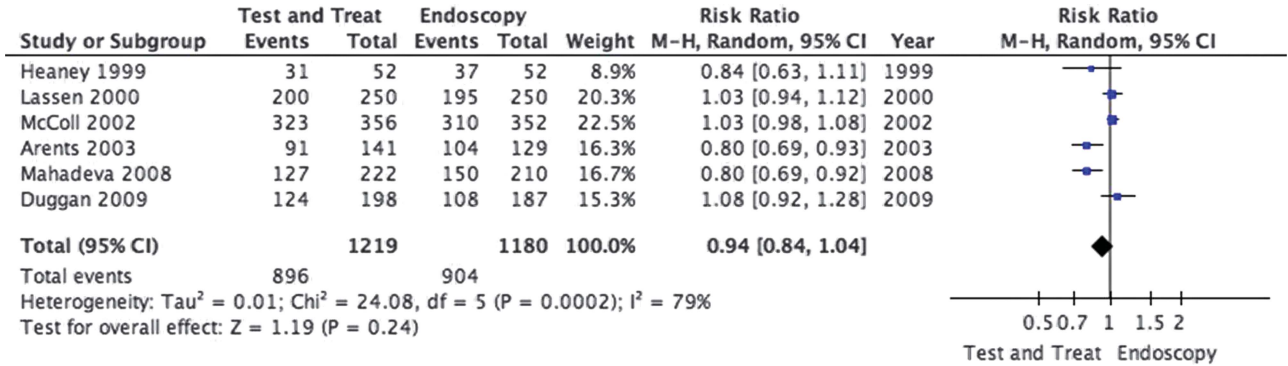


Figure 2. Forest plot of randomized controlled trials comparing *H. pylori* test and treat with early endoscopy with proportion having endoscopy as the outcome.

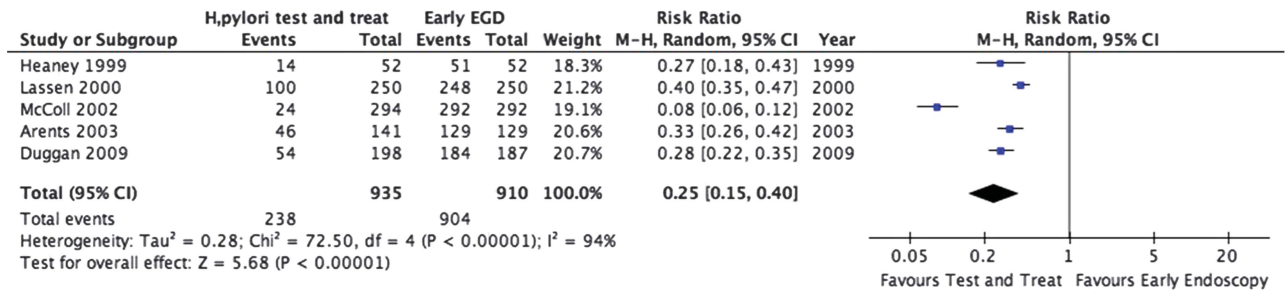


Figure 3. Forest plot of randomized controlled trials comparing *H. pylori* test and treat with early endoscopy with dyspepsia health service costs as the outcome.

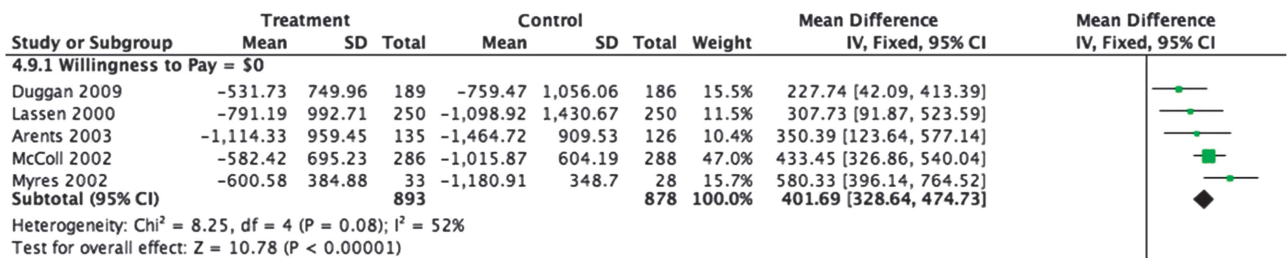


Figure 4. Forest plot of randomized controlled trials comparing *H. pylori* eradication with placebo antibiotics in infected dyspepsia patients.

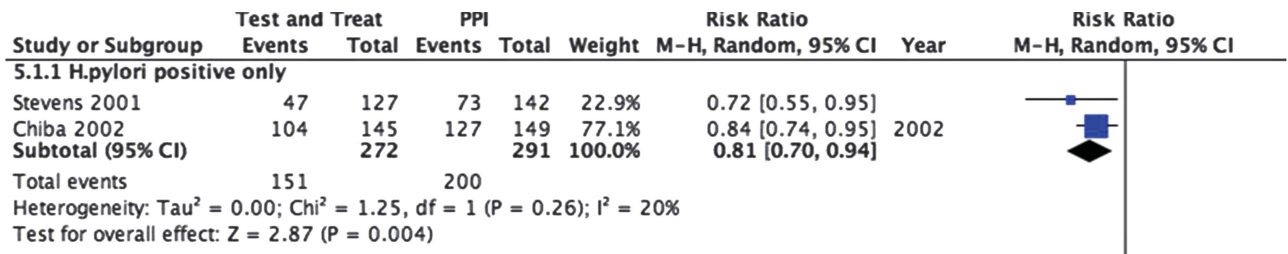


Figure 5. Forest plot of randomized controlled trials comparing *H. pylori* test and treat with empirical PPI therapy with continued dyspepsia as the outcome.

**5.1.2 All patients randomised before testing**

Study	Events	Total	Events	Total	Weight	Risk Ratio	95% CI	Year
Manes 2003	61	110	96	109	21.4%	0.63	[0.53, 0.75]	2003
Jarbol 2006	195	250	181	222	27.4%	0.96	[0.87, 1.05]	2006
Delaney 2008	217	265	229	276	28.1%	0.99	[0.91, 1.07]	2008
Duggan 2009	124	198	110	178	23.1%	1.01	[0.87, 1.19]	2009
<b>Subtotal (95% CI)</b>		<b>823</b>		<b>785</b>	<b>100.0%</b>	<b>0.89</b>	<b>[0.77, 1.04]</b>	
Total events	597		616					
Heterogeneity: Tau <sup>2</sup> = 0.02; Chi <sup>2</sup> = 21.65, df = 3 (P < 0.0001); I <sup>2</sup> = 86%								
Test for overall effect: Z = 1.41 (P = 0.16)								

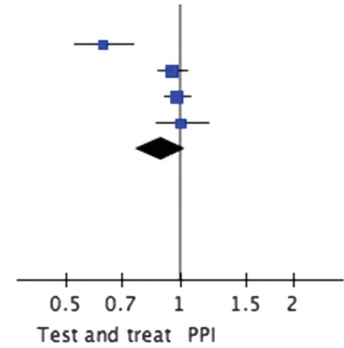


Figure 6. Forest plot of randomized controlled trials comparing empirical PPI therapy with placebo with continued dyspepsia as the outcome.

Study or Subgroup	PPI		Antacide/alginat		Weight	Risk Ratio		Year	Risk Ratio
	Events	Total	Events	Total		M-H, Random, 95% CI	M-H, Random, 95% CI		
<b>1.1.1 Global assessment of dyspepsia (primary outcome most stringent definition of Not symptom-free)</b>									
Meineche-Schmidt 1997	136	273	173	266	17.4%	0.77	[0.66, 0.89]	1997	
Goves 1998	197	333	285	337	18.9%	0.70	[0.63, 0.77]	1998	
Rabeneck 2002	37	71	41	69	12.0%	0.88	[0.65, 1.18]	2002	
Meineche-Schmidt 2004	196	556	177	272	17.6%	0.54	[0.47, 0.62]	2004	
Veldhuyzen van Zanten 2005	75	135	87	133	15.7%	0.85	[0.70, 1.03]	2005	
Baysal 2015	102	132	114	132	18.5%	0.89	[0.80, 1.00]	2015	
<b>Subtotal (95% CI)</b>		<b>1500</b>		<b>1209</b>	<b>100.0%</b>	<b>0.75</b>	<b>[0.64, 0.88]</b>		
Total events	743		877						
Heterogeneity: Tau <sup>2</sup> = 0.03; Chi <sup>2</sup> = 34.83, df = 5 (P < 0.00001); I <sup>2</sup> = 86%									
Test for overall effect: Z = 3.49 (P = 0.0005)									

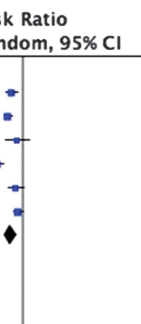


Figure 7. Forest plot of randomized controlled trials comparing empirical PPI therapy with H<sub>2</sub>-receptor antagonists with continued dyspepsia as the outcome.

Study or Subgroup	PPI		H2RA		Weight	Risk Ratio		Year	Risk Ratio
	Events	Total	Events	Total		M-H, Random, 95% CI	M-H, Random, 95% CI		
<b>1.2.1 Global assessment of dyspepsia (Primary outcome most stringent definition of non-resolution/non improvement)</b>									
Meineche-Schmidt 1997	110	207	147	220	14.9%	0.80	[0.68, 0.93]	1997	
Jones 1997	118	213	155	219	15.0%	0.78	[0.68, 0.91]	1997	
Mason 1998	141	363	222	362	15.0%	0.63	[0.54, 0.74]	1998	
Veldhuyzen van Zanten 2005	75	135	82	139	14.1%	0.94	[0.77, 1.16]	2005	
Dewan 2011	77	101	31	101	12.0%	2.48	[1.82, 3.40]	2011	
Sakurai 2012	105	142	120	132	15.5%	0.81	[0.73, 0.91]	2012	
Maity 2014	43	61	42	61	13.5%	1.02	[0.81, 1.29]	2014	
<b>Subtotal (95% CI)</b>		<b>1222</b>		<b>1234</b>	<b>100.0%</b>	<b>0.93</b>	<b>[0.76, 1.16]</b>		
Total events	669		799						
Heterogeneity: Tau <sup>2</sup> = 0.07; Chi <sup>2</sup> = 65.00, df = 6 (P < 0.00001); I <sup>2</sup> = 91%									
Test for overall effect: Z = 0.62 (P = 0.53)									

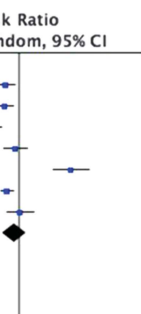


Figure 8. Forest plot of randomized controlled trials comparing empirical acid suppression therapy with early endoscopy with continued dyspepsia as the outcome.

Study or Subgroup	Prompt EGD		Empirical therapy		Weight	Risk Ratio		Year
	Events	Total	Events	Total		M-H, Random, 95% CI	M-H, Random, 95% CI	
Bytzer 1994	168	208	165	206	31.2%	1.01	[0.92, 1.11]	1994
Delaney 2000	201	256	139	186	25.4%	1.05	[0.95, 1.17]	1999
Lewin-van den Broek 2001	36	79	48	84	3.1%	0.80	[0.59, 1.08]	2001
Kjeldsen 2007	149	184	152	184	30.3%	0.98	[0.89, 1.08]	2007
Duggan 2009	108	187	110	178	9.9%	0.93	[0.79, 1.11]	2009
<b>Total (95% CI)</b>		<b>914</b>		<b>838</b>	<b>100.0%</b>	<b>1.00</b>	<b>[0.94, 1.05]</b>	
Total events	662		614					
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 3.95, df = 4 (P = 0.41); I <sup>2</sup> = 0%								
Test for overall effect: Z = 0.17 (P = 0.87)								

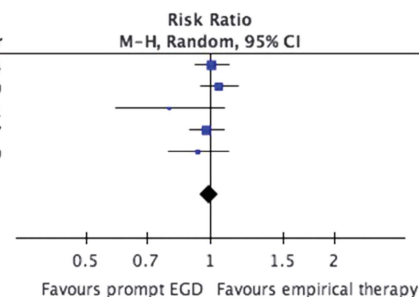




Figure 9. Forest plot of randomized controlled trials comparing empirical PPI therapy with prokinetic therapy with continued dyspepsia as the outcome.

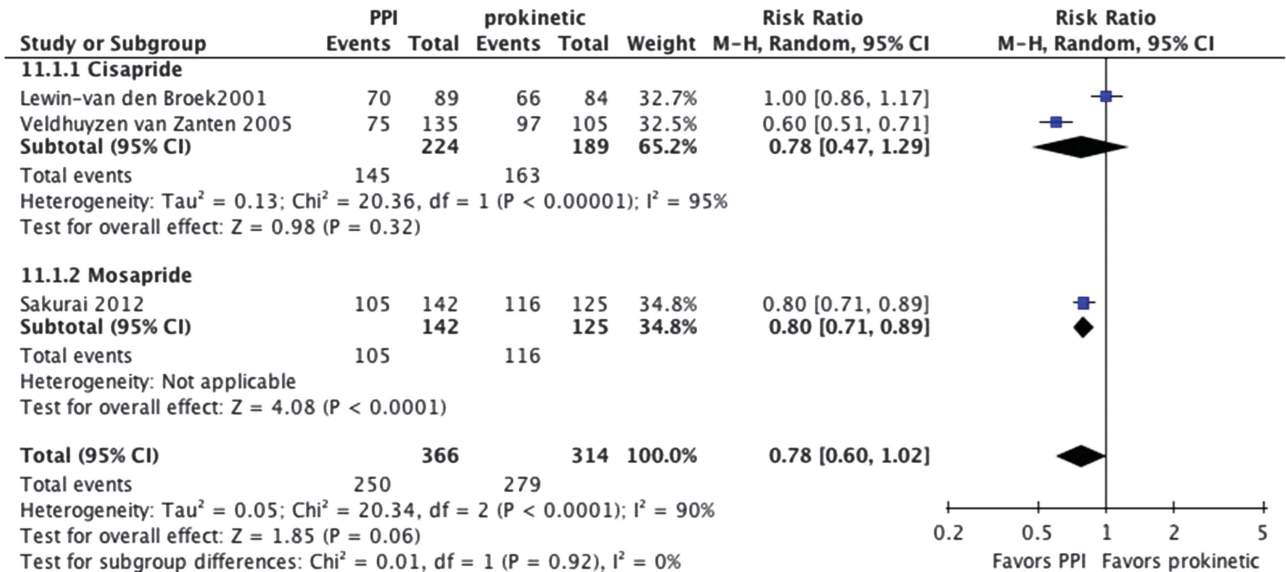


Figure 10. Forest plot of randomized controlled trials comparing *H. pylori* eradication with placebo antibiotics in *H. pylori*-infected patients with functional dyspepsia.

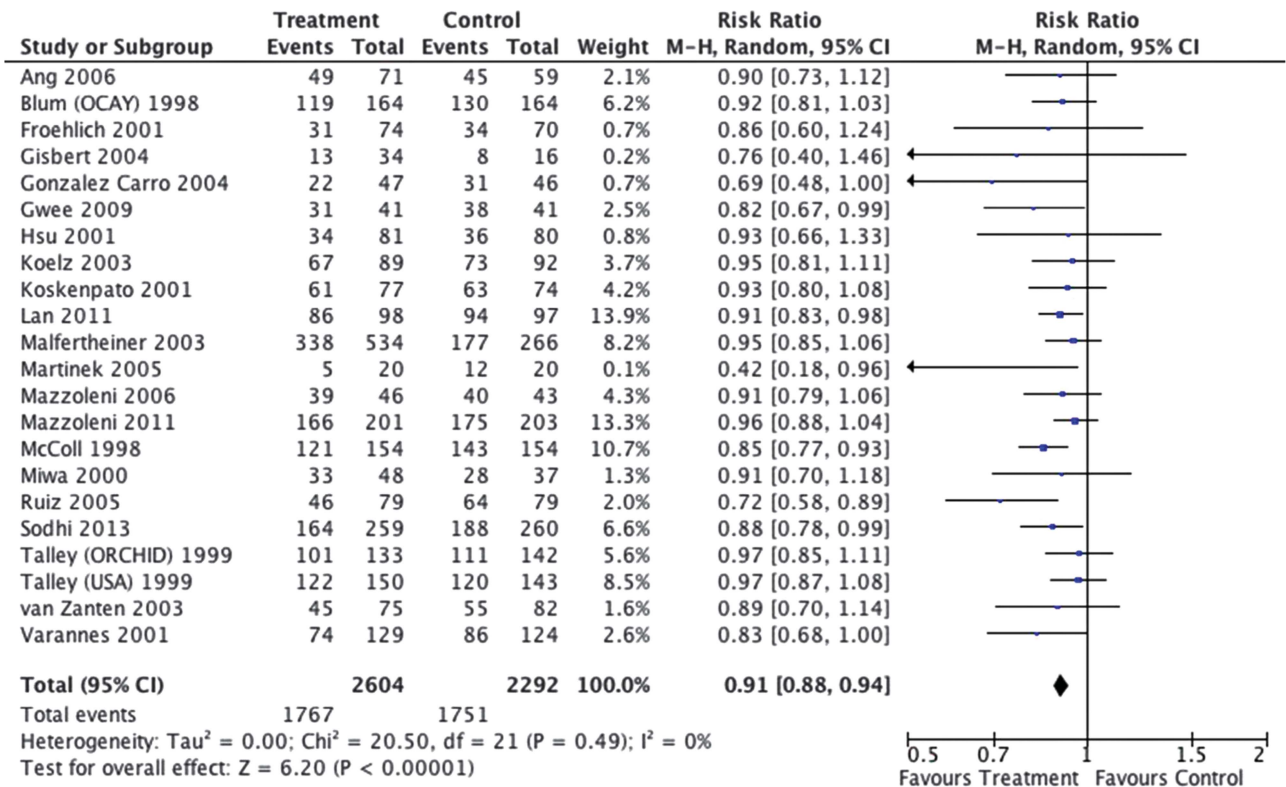




Figure 11. Forest plot of randomized controlled trials comparing proton pump inhibitors with placebo in functional dyspepsia patients.

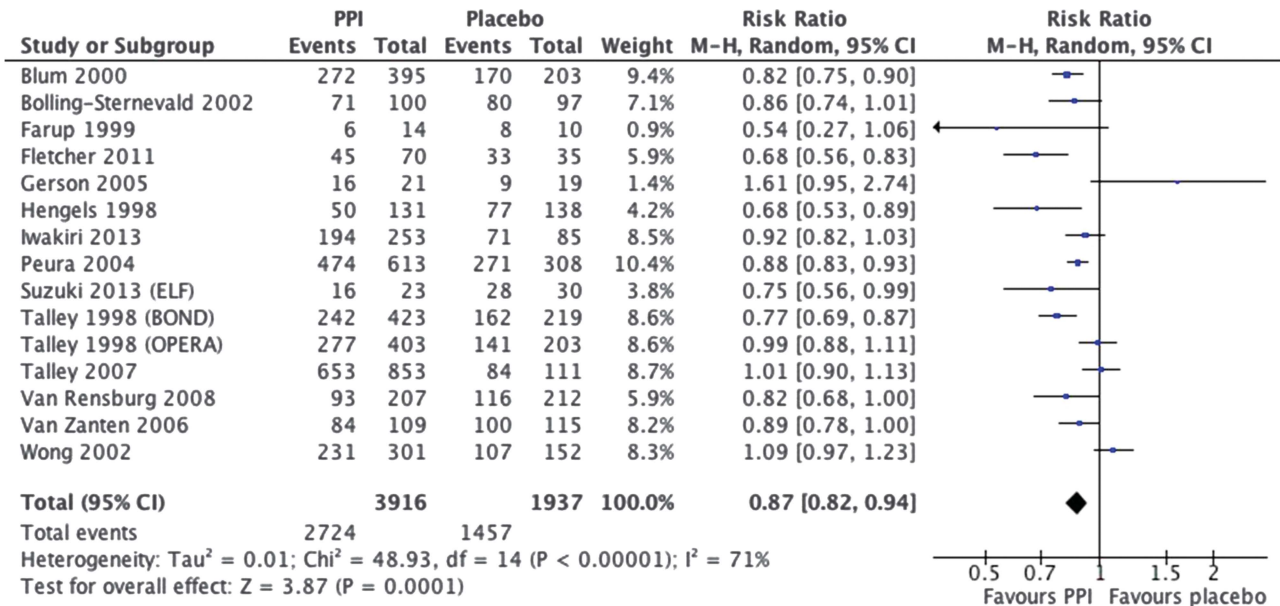


Figure 12. Forest plot of randomized controlled trials comparing proton pump inhibitors with prokinetics in functional dyspepsia patients.

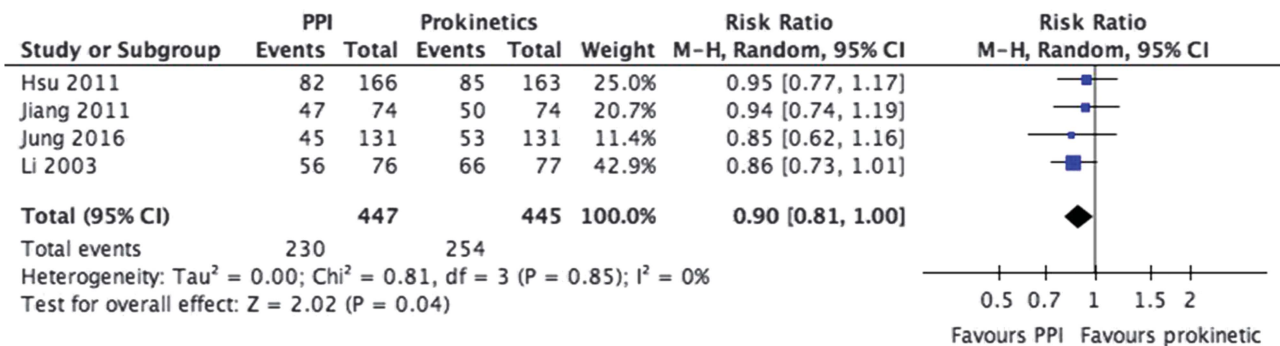


Figure 13. Forest plot of randomized controlled trials comparing motility modifying drugs with placebo in functional dyspepsia patients.

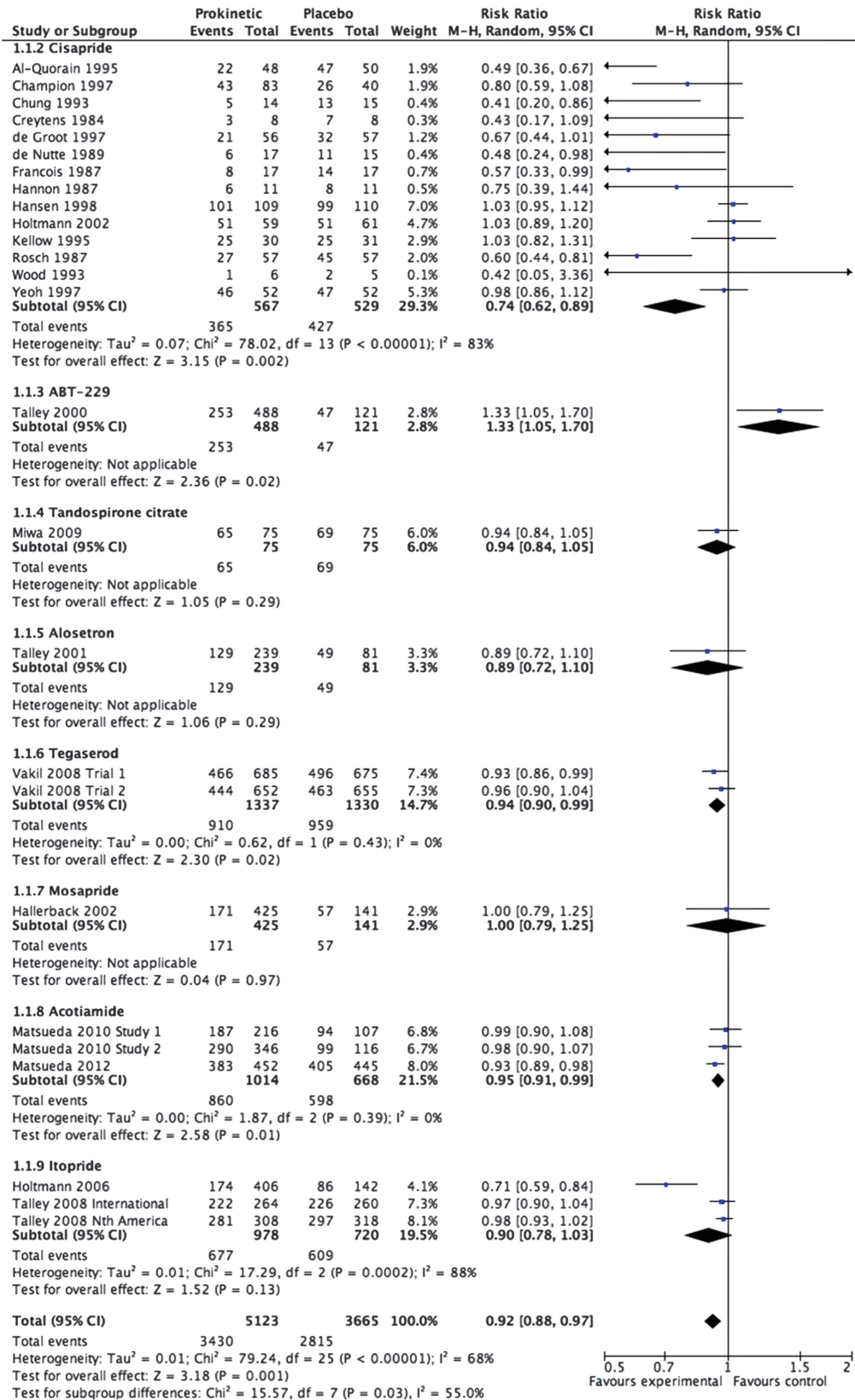


Figure 14. Forest plot of randomized controlled trials comparing domperidone with placebo in patients with upper GI symptoms.

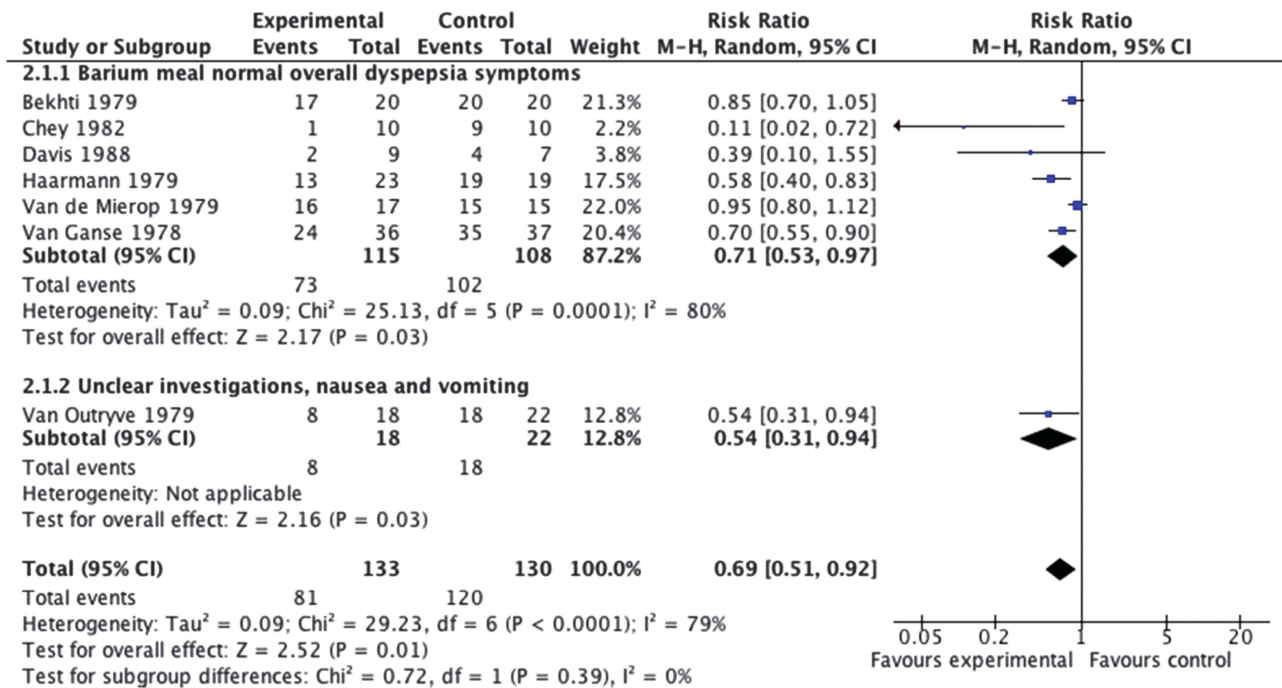


Figure 15. Forest plot of randomized controlled trials comparing psychological therapies with controls in functional dyspepsia patients.

