CME

ACG and CAG Clinical Guideline: Management of Dyspepsia

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We have updated both the American College of Gastroenterology (ACG) and the Canadian Association of Gastroenterology (CAG) guidelines on dyspepsia in a joint ACG/CAG dyspepsia guideline. We suggest that patients ≥60 years of age presenting with dyspepsia are investigated with upper gastrointestinal endoscopy to exclude organic pathology. This is a conditional recommendation and patients at higher risk of malignancy (such as spending their childhood in a high risk gastric cancer country or having a positive family history) could be offered an endoscopy at a younger age. Alarm features should not automatically precipitate endoscopy in younger patients but this should be considered on a case-by-case basis. We recommend patients <60 years of age have a non-invasive test *Helicobacter pylori* and treatment if positive. Those that are negative or do not respond to this approach should be given a trial of proton pump inhibitor (PPI) therapy. If these are ineffective tricyclic antidepressants (TCA) or prokinetic therapies can be tried. Patients that have an endoscopy where no pathology is found are defined as having functional dyspepsia (FD). *H. pylori* eradication should be offered in these patients if they are infected. We recommend PPI, TCA and prokinetic therapy (in that order) in those that fail therapy or are *H. pylori* negative. We do not recommend routine upper gastrointestinal (GI) motility testing but it may be useful in selected patients.

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INTRODUCTION

Descriptions of upper gastrointestinal symptoms date back thousands of years (1). "Stomach disorders" became an obsession of developed countries in the eighteenth century (2) when the term dyspepsia was first coined (3). A systematic review (4) reported that ~20% of the population has symptoms of dyspepsia globally. Dyspepsia is more common in women, smokers, and those taking non-steroidal anti-inflammatory drugs (4). Patients with dyspepsia have a normal life expectancy (5), however, symptoms negatively impact on quality of life (6,7) and there is a significant economic impact to the health service and society (8). Dyspepsia is estimated to cost the US health care service over $18 billion per annum (8) and societal costs are likely to be double this (9) with 2–5% (refs 7,9) having time off work because of symptoms. Cost-effective management of dyspepsia can reduce its health and economic burdens, but it is over 10 years since either the American College of Gastroenterology (ACG) (10) or Canadian Association of Gastroenterology (CAG) (11) published guidelines on dyspepsia. We have therefore updated previous systematic review data (12) for a joint ACG and CAG guideline on dyspepsia management.

DEFINITION OF DYSPEPSIA AND SCOPE OF THE GUIDELINE

Dyspepsia was originally defined as any symptoms referable to the upper gastrointestinal tract (13). The Rome committee has developed iterative definitions of dyspepsia that have become more specific culminating in Rome IV (ref. 14). These definitions have attempted to minimize the inclusion of gastro-esophageal reflux disease in those with dyspepsia by excluding patients with heartburn and acid regurgitation (15). Rome definitions have been helpful in better-standardizing patients that are included in studies of dyspepsia but are less relevant to clinical practice as there is considerable overlap in symptom presentation (16) making classification difficult in many patients presenting in primary and secondary care. For this reason, we have used a clinically relevant definition of dyspepsia as predominant epigastric pain

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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**.

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 *H. pylori*, and therapy for *H. pylori* 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 *H. pylori*-negative or who remain symptomatic after *H. pylori* eradication therapy. Strong recommendation, high quality evidence.
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.
6. We suggest dyspepsia patients under the age of 60 not responding to PPI or *H. pylori* eradication therapy should be offered TCA therapy. Conditional recommendation low quality evidence.
7. We recommend FD patients that are *H. pylori* positive should be prescribed therapy to treat the infection. Strong recommendation, high quality evidence.
8. We recommend FD 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.
9. We recommend FD patients not responding to PPI or *H. pylori* eradication therapy (if appropriate) should be offered TCA therapy. Conditional recommendation, moderate quality evidence.
10. We suggest FD patients not responding to PPI, *H. pylori* 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; *H. pylori*, *Helicobacter pylori*; PPI, proton pump inhibitor; TCA, tricyclic antidepressant.

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 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 *H. pylori* test and treat the most appropriate initial strategy for patients <60 years of age with dyspepsia?	Adult uninvestigated dyspepsia patients	*H. pylori* 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 *H. pylori* negative or remain symptomatic after eradication therapy?	Adult uninvestigated dyspepsia patients	Empirical PPI therapy	1. Placebo 2. Do nothing 3. H_2RA 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 *H. pylori* 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 *H. pylori* 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 *H. pylori* eradication therapy in *H. pylori*-positive patients effective in reducing symptoms of FD?	Adult dyspepsia patients with predominant epigastric pain/discomfort and a normal EGD that are *H. pylori* positive	*H. pylori* 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_2RA 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_2RA, H_2-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 imagining 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 pretest 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 >20 lb 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_2-receptor antagonist (H_2RA). 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_2RA in providing symptom relief (RR=0.93; 95% CI=0.76–1.16) with a large amount of heterogeneity among studies (I^2=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					Effect per 1,000 patients tested	Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Pre-test probability of 0.3%	
True positives (patients with upper GI cancer)	7 studies 150 patients	Cross-sectional (cohort type accuracy study)	Not serious	Not serious	Serious[a]	Not serious	None	2 (2–2)	⊕⊕⊕O 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[a]	Not serious	None	658 (548–788)	⊕⊕⊕O 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%.
[a]Significant unexplained heterogeneity between studies.

(57,63) showed no significant difference between both groups and one trial showed a benefit of H_2RA (ref. 61). This trial (61) evaluated an H_2RA not available in the West. It is not biologically plausible that H_2RA would be more effective than PPI therapy; if this trial is excluded there is a significant benefit of PPI over H_2RA (RR remaining dyspeptic=0.81; 95% CI=0.72–0.91). There is not a major difference in cost between H_2RA and PPI therapy and the group felt the balance of evidence supported empirical PPI over H_2RA 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_2RA 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

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	Relative (95% CI)	Absolute (95% CI)		
H. pylori test and treat vs. endoscopy: dyspepsia outcome (follow up: median 1 years; assessed with: questionnaire)												
6	Randomized trials	Serious[a]	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
H. pylori test and treat vs. endoscopy: health-related dyspepsia costs (US $) (follow up: median 1 years; assessed with: questionnaire)												
5	Randomized trials	Serious[a]	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[b]	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[b]	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[c]	Serious[d]	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.
[a]All trials high risk of bias as blinding not possible.
[b]Significant unexplained heterogeneity with I^2>50%.
[c]Patients had FD and not uninvestigated dyspepsia. We are assuming most patients will have FD.
[d]95% CI are relatively wide as only based on three studies.

Table 5. Summary of findings table for interventions for FD

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	Relative (95% CI)	Absolute (95% CI)		
H. pylori eradication vs. placebo antibiotics in *H. pylori* +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[a]	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[b]	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[a]	Not serious	Serious[c]	Publication bias strongly suspected[d]	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[e]	Serious[a]	Not serious	Serious[f]	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.
[a]Unexplained heterogeneity with I^2>50%.
[b]Wide 95% CI as based on three trials.
[c]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.
[d]Strong funnel plot asymmetry with small trials showing large effect and many large trials negative.
[e]Studies not blinded and outcome subjective.
[f]Wide 95% CI and only two RCTs for any type of intervention.

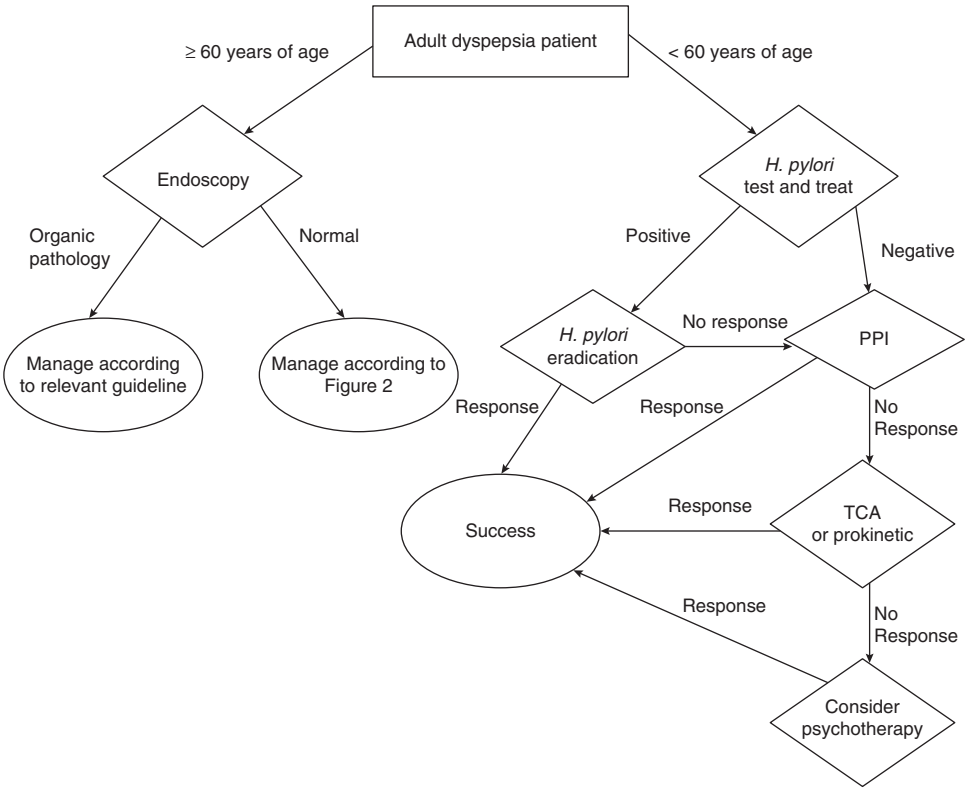

Figure 1. Algorithm for the management of undiagnosed dyspepsia.

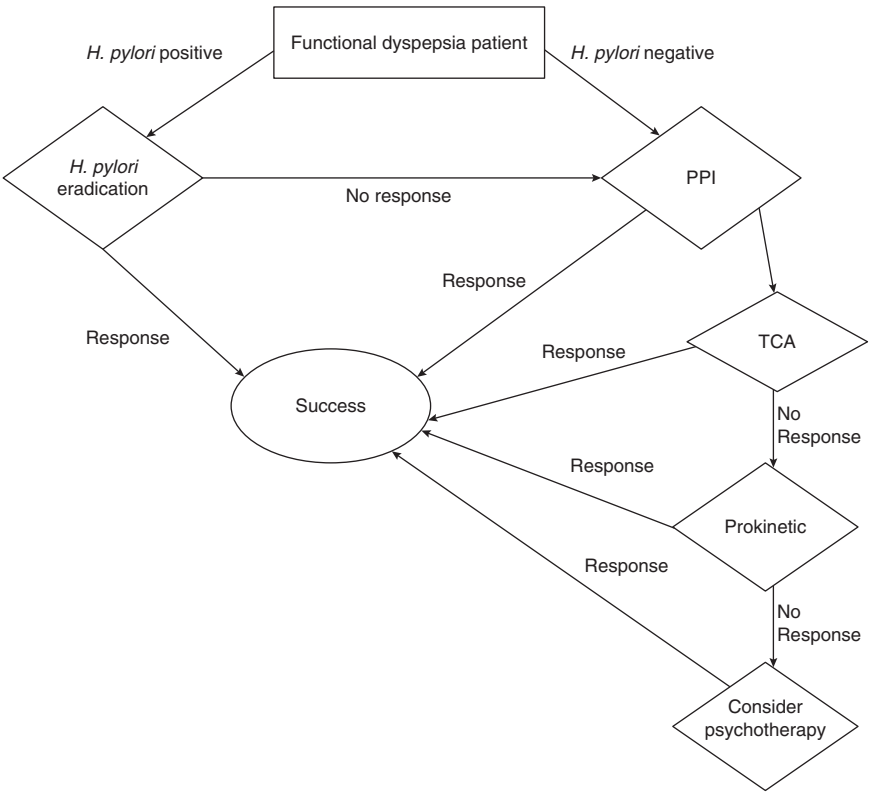

Figure 2. Algorithm for the treatment of functional dyspepsia.

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 extensively 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±4.8 in the STW 5 group compared with 5.9±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 4 h) (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, FACG.

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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APPENDIX 1

SEARCH STRATEGIES USED FOR THE DYSPEPSIA 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	1 exp Dyspepsia/ (7,888) 2 eructation/ (328) 3 flatulence/ (1,301) 4 (dyspep* or "NUD" or "FD").mp. (20,895) 5 (indigestion or indigestive).tw,kw. (799) 6 1 or 2 or 3 or 4 or 5 (22,982) 7 exp Psychotherapy/(167,526) 8 psychotherap*.af. (103,197) 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*) adj5 (therap* or treat* or manag* or strategy*)).tw,kw. (67,724) 10 ((horticultural or socioenvironmental or social environment or socio* environment or logotherap* or reality or gestalt) adj5 (therap* or treat* or manag* or strategy*)).tw,kw. (2,178) 11 (autogenic training or (relaxation adj2 progressive) or bibliotherap* or hypnosis or hypnoses or hypnotherap* or hypnotism or mesmerism or abreaction or catharsis).tw,kw. (9,967) 12 or/7–11 (254,628) 13 6 and 12 (253) 14 randomized controlled trial.pt. (416,221) 15 controlled clinical trial.pt. (90,701) 16 random*.mp. (1,046,809) 17 placebo.ab. (171,882) 18 trial.ab. (364,897) 19 groups.ab. (1,579,013) 20 or/14–19 (2,535,619) 21 13 and 20 (78) 22 limit 21 to yr="2005 -Current" (42)	1 exp Dyspepsia/ (28,265) 2 eructation/ (983) 3 flatulence/ (9,815) 4 (dyspep* or "NUD" or "FD").mp. (42,121) 5 (indigestion or indigestive).tw,kw. (1,203) 6 1 or 2 or 3 or 4 or 5 (52,030) 7 exp Psychotherapy/(209,526) 8 psychotherap*.af. (139,519) 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*) adj5 (therap* or treat* or manag* or strategy*)).tw,kw. (95,906) 10 ((horticultural or socioenvironmental or social environment or socio* environment or logotherap* or reality or gestalt) adj5 (therap* or treat* or manag* or strategy*)).tw,kw. (3,158) 11 (autogenic training or (relaxation adj2 progressive) or bibliotherap* or hypnosis or hypnoses or hypnotherap* or hypnotism or mesmerism or abreaction or catharsis).tw,kw. (12,483) 12 or/7–11 (332,259) 13 6 and 12 (1,203) 14 random*.mp. (1,250,429) 15 clinical trial:.mp. (1,213,928) 16 exp health care quality/ (2,307,441) 17 double-blind:.mp. or placebo:.tw. or blind:.tw. (462,289) 18 or/14–17 (4,013,838) 19 13 and 18 (766) 20 limit 19 to yr="2005 -Current" (602)
Prokinectis and FD from 2010 to 12 April 2016, Multi-file search, *n*=1,026	1 exp Dyspepsia/7,859 2 (dyspep* or "NUD" or "FD").tw,kw. 18,461 3 (indigestion or indigestive).tw. 783 4 or/1–3 20,884 5 (prokinetic* or gastroprokinetic* or gastrokinetic* or gastro-kinetic*).tw,kw. 2,687 6 (antiemetic* or anti-emetic).tw,kw. 7,327 7 exp Benzamides/46,246 8 (Benzoic Acid Amide or Amides or Phenyl Carboxyamide or Benzamide* or Benzoylamide or benzoates).tw,kw. 13,430 9 (Phenylcarboxyamide or Phenylcarboxamide or Benzenecarboxamide or Amid kyseliny benzoove).tw,kw. 12 10 exp Domperidone/1,623 11 (domperidon* or domidon or Domperi or Domstal or evoxin or gastrocure or motilium or motilium).tw,kw. 2,103 12 (motis or nauzelin or Motinorm Costi or Nomit or Brulium or Molax).tw,kw. 4 13 exp Antiemetics/133,454 14 exp Metoclopramide/4,630 15 (Metoclopramide or cerucal or clopra or gastrese or gastrobid or gastroflux or gastromax or maxolon).tw,kw. 5,414 16 (metaclopramide or metozolv or metramid or migravess or mygdalon or octamide or parmid).tw,kw. 45 17 (primperan or reglan or reliveran or rimetin or Degan or Maxeran or Pylomid or Pramin).tw,kw. 115 18 exp Cisapride/1,444 19 (Cisapride or alimix or Prepulsid or Propulsid).tw,kw. 1,675 20 exp Cholinesterase Inhibitors/44,836	1 exp dyspepsia/28,132 2 (dyspep* or "NUD" or "FD").tw,kw. 26,029 3 (indigestion or indigestive).tw. 1,188 4 or/1–3 42,564 5 (prokinetic* or gastroprokinetic* or gastrokinetic* or gastro-kinetic*).tw,kw. 4,035 6 (antiemetic* or anti-emetic).tw,kw. 10,216 7 exp benzamide derivative/54,971 8 (Benzoic Acid Amide or Amides or Phenyl Carboxyamide or Benzamide* or Benzoylamide or benzoates).tw,kw. 16,902 9 (Phenylcarboxyamide or Phenylcarboxamide or Benzenecarboxamide or Amid kyseliny benzoove).tw,kw. 13 10 exp domperidone/7,795 11 (domperidon* or domidon or Domperi or Domstal or evoxin or gastrocure or motilium or motilium).tw,kw. 3,417 12 (motis or nauzelin or Motinorm Costi or Nomit or Brulium or Molax).tw,kw. 16 13 exp antiemetic agent/168,619 14 exp metoclopramide/22,515 15 (Metoclopramide or cerucal or clopra or gastrese or gastrobid or gastroflux or gastromax or maxolon).tw,kw. 7,192 16 (metaclopramide or metozolv or metramid or migravess or mygdalon or octamide or parmid).tw,kw. 114 17 (primperan or reglan or reliveran or rimetin or Degan or Maxeran or Pylomid or Pramin).tw,kw. 1,692 18 exp cisapride/7,296 19 (Cisapride or alimix or Prepulsid or Propulsid).tw,kw. 2,729 20 exp cholinesterase inhibitor/77,946

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
	21 (Itopride or ganaton).tw,kw. 102 22 Mosapride.tw,kw. 262 23 exp Erythromycin/22,427 24 (erythromycin or aknemycin or emcin or emgel or emycin or eryderm or erygel or erymax).tw,kw. 18,745 25 (erymin or eryped or gallimycin or ilosene or ilosone or ilotycin or lauromicina or maracyn).tw,kw. 60 26 (monomycin or ornacyn or retcin or rommix or romycin or roymicin or staticin or stiemycin or theramycin or tiloryth or wyamycin).tw,kw. 275 27 (Motilin adj3 (receptor* or agonist*)).tw,kw. 369 28 ((5HT3 or 5HT 3 or 5-HT3 or 5-HT 3) adj3 antagonist*).tw,kw. 3,638 29 ((5HT or 5-HT or 5-hydroxytryptamine*) adj3 (agonist* or antagonist*)).tw,kw. 8,795 30 ((5-HT1A or 5HT1A or 5-HT 1A or 5HT 1A) adj3 agonist*).tw,kw. 4,069 31 exp Serotonin Antagonists/47,240 32 exp Serotonin 5-HT3 Receptor Antagonists/612 33 exp Serotonin 5-HT4 Receptor Agonists/224 34 exp Serotonin 5-HT1 Receptor Agonists/2,887 35 (serotonin adj3 receptor adj3 (agonist* or antagonist* or block*)).tw,kw. 2,068 36 (tegaserod or Zelnorm or Zelmac).tw,kw. 388 37 ABT-229.tw,kw. 22 38 (Tandospirone or Sediel or metanopirone or buspirone).tw,kw. 2,603 39 (alosetron or Lotronex).tw,kw. 245 40 (Acotiamide or YM-443 or Z-338D).tw,kw. 40 41 (acetylcholinesterase inhibitor* or cholinesterase Inhibitor* or anti-cholinesterase* or anticholinesterase*).tw,kw. 10,393 42 ((5HT-4 or 5HT4 or 5-HT 4 or 5-HT4) adj3 agonist*).tw,kw. 740 43 or/5–42 316,333 44 4 and 43 1,331 45 randomized controlled trial.pt. 412,566 46 controlled clinical trial.pt. 90,495 47 random*.mp. 1,019,981 48 placebo.ab. 168,576 49 drug therapy.fs. 1,841,827 50 trial.ab. 354,331 51 groups.ab. 1,539,040 52 or/45–51 3,918,006 53 exp animals/ not humans.sh. 4,221,321 54 52 not 53 3,364,132 55 44 and 54 1,058 56 limit 55 to yr="2010 -Current" 221	21 (Itopride or ganaton).tw,kw. 226 22 exp mosapride/380 23 Mosapride.tw,kw. 469 24 exp erythromycin/66,403 25 (erythromycin or aknemycin or emcin or emgel or emycin or eryderm or erygel or erymax).tw,kw. 22,087 26 (erymin or eryped or gallimycin or ilosene or ilosone or ilotycin or lauromicina or maracyn).tw,kw. 275 27 (monomycin or ornacyn or retcin or rommix or romycin or roymicin or staticin or stiemycin or theramycin or tiloryth or wyamycin).tw,kw. 271 28 exp motilin receptor agonist/69,135 29 (Motilin adj3 (receptor* or agonist*)).tw,kw. 458 30 ((5HT3 or 5HT 3 or 5-HT3 or 5-HT 3) adj3 antagonist*).tw,kw. 4,824 31 ((5HT or 5-HT or 5-hydroxytryptamine*) adj3 (agonist* or antagonist*)).tw,kw. 9,448 32 ((5-HT1A or 5HT1A or 5-HT 1A or 5HT 1A) adj3 agonist*).tw,kw. 4,827 33 exp serotonin antagonist/120,230 34 exp serotonin 3 antagonist/3,440 35 exp serotonin 4 agonist/802 36 exp serotonin 1 agonist/610 37 (serotonin adj3 receptor adj3 (agonist* or antagonist* or block*)).tw,kw. 2,790 38 exp tegaserod/ 1,705 39 (tegaserod or Zelnorm or Zelmac).tw,kw. 737 40 ABT-229.tw,kw. 98 41 exp tandospirone/519 42 (Tandospirone or Sediel or metanopirone or buspirone).tw,kw. 3,272 43 exp alosetron/1,233 44 (alosetron or Lotronex).tw,kw. 541 45 exp acotiamide/105 46 (Acotiamide or YM-443 or Z-338D).tw,kw. 77 47 (acetylcholinesterase inhibitor* or cholinesterase Inhibitor* or anti-cholinesterase* or anticholinesterase*).tw,kw. 13,960 48 ((5HT-4 or 5HT4 or 5-HT 4 or 5-HT4) adj3 agonist*).tw,kw. 1,013 49 or/5–48 452,852 50 4 and 49 3,919 51 random*.mp. 1,239,350 52 placebo:.mp. 372,038 53 clinical trial:.mp. 1,207,584 54 double-blind:.mp. or blind:.tw. 354,000 55 or/51–54 2,210,439 56 exp animal/ not human/4,594,892 57 55 not 56 2,042,185 58 50 and 57 2,204 59 remove duplicates from 58 2,189 60 limit 59 to yr="2010 -Current" 639
HP eradication and HP from 2006 to 4 April 2016, Multi-file search, *n*=1,170	1 randomized controlled trial.pt. (338,380) 2 controlled clinical trial.pt. (85,027) 3 random*.mp. (793,630) 4 placebo.ab. (139,962) 5 drug therapy.fs. (1,570,375) 6 trial.ab. (263,685) 7 groups.ab. (1,213,517) 8 1 or 2 or 3 or 4 or 5 or 6 or 7 (3,196,892) 9 exp animals/ not exp humans/(3,749,652)	1 clinical trial/ or (clin$ adj2 (trial$ or stud$)).tw. 2 exp Randomized controlled trial/ 3 exp Randomization/ 4 Single-Blind Method/ 5 Double-Blind Method/ 6 Cross-Over Studies/ or (crossover$ or cross-over$).tw. 7 exp Random Allocation/ 8 RCT.tw. 9 ((single or double or treble or triple) adj3 (blind$ or mask$)).tw.

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
	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 *helicobacter pylori*/(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)	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$).tw. 17 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 14 or 16 18 exp animal/not exp human/ 19 17 not 18 20 exp dyspepsia/ 21 eructation/ 22 flatulence/ 23 (dyspepsia or dyspeptic or NUD or FD).mp. 24 (indigestion or indigestive).tw. 25 20 or 21 or 22 or 23 or 24 26 exp Helicobacter/ 27 exp *Helicobacter pylori*/ 28 exp Helicobacter infection/ 29 (helicobacter or pylori or pyloridis or HP or Campylobacter).mp. 30 26 or 27 or 28 or 29 31 25 and 30 32 19 and 31 (3,551) 33 limit 32 to yr="2006 -Current" (1,237)
PPI and FD from 2002 to 25 Feb 2016, Multi-file search, *n*=2,670 search in 11 April 2013, *n*=527 update search in 2016	1. exp dyspepsia/ 2. (Dyspepsia or dyspeptic or NUD or FD).mp. 3. (indigestion or indigestive).tw. 4. or/1–3 5. exp Proton Pump Inhibitors/ 6. ((proton adj2 pump adj2 inhibitor$) 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 losec or nexium or prilosec or rapinex or zegerid or ocid or Lomac or Omepral or Omez).tw. 11. (pantoprazole or protium or protonix or Pantotab or Pantopan or Pantozol or Pantor or Pantoloc or Astropan or Controloc or Pantecta or Inipomp or Somac or Pantodac or Zurcal or Zentro).tw. 12. (rabeprazole or aciphex or dexrabeprazole or pariet or Zechin or Rabecid or Nzole-D or Rabeloc).tw. 13. (Dexlansoprazole or Kapidex or Dexilant).tw. 14. (lansoprazole or lanzoprazole or agopton or bamalite or Inhibitol or Levant or Lupizole or lanzor or monolitum or ogast or ogastro or opiren or prevacid or prezal or pro ulco or promeco or takepron 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	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 losec or nexium or prilosec or rapinex or zegerid or lomac or ocid or Lomac or Omepral or Omez).tw. 11. pantoprazole/ 12. (pantoprazole or protium or protonix or Pantotab or Pantopan or Pantozol or Pantor 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 dexrabeprazole or pariet or Zechin or Rabecid or Nzole-D or Rabeloc).tw. 15. lansoprazole/ 16. (lansoprazole or lanzoprazole or agopton or bamalite or Inhibitol or Levant or Lupizole or lanzor or monolitum or ogast 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

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
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	1 exp dyspepsia/ (7,282) 2 (dyspep* or FD or NUD).ti,ab,kw. (10,750) 3 1 or 2 (12,551) 4 exp Proton Pump Inhibitors/ (14,111) 5 exp omeprazole/ (8,570)	1 exp dyspepsia/ (25,632) 2 (dyspep* or FD or NUD).ti,ab,kw. (14,899) 3 1 or 2 (29,332) 4 exp proton pump inhibitor/ (52,191) 5 exp omeprazole/ (26,121)
	6 exp esomeprazole/(691) 7 exp lansoprazole/(1,848) 8 exp rabeprazole/(795) 9 (proton pump inhibitor* or PPI or PPIs or omeprazole or esomeprazole or lansoprazole or pantoprazole or rabeprazole).ti,ab,kw. (22,117) 10 or/4–9 (25,881) 11 exp Histamine H_2 Antagonists/(18,410) 12 exp ranitidine/(4,990) 13 exp cimetidine/(9,164) 14 exp famotidine/(1,480) 15 exp nizatidine/(300) 16 ((histamine H_2 adj5 antagonist*) or H_2-receptor antagonist* or H_2RA or H_2RAs or H_2-RA or H_2-RAs or cimetidine or ranitidine or famotidine or nizatidine or roxatidine).ti,ab,kw. (18,135) 17 or/11–16 (23,248) 18 exp Helicobacter/ or exp *Helicobacter pylori*/ or exp Helicobacter infection/ (31,400) 19 (helicobacter or pylori or pyloridis or "HP" or Campylobacter).ti,ab,kw. (59,887)	6 exp esomeprazole/(5,198) 7 exp lansoprazole/(8,781) 8 exp pantoprazole/(6,458) 9 exp rabeprazole/ (3,819) 10 (proton pump inhibitor* or PPI or PPIs or omeprazole or esomeprazole or lansoprazole or pantoprazole or rabeprazole).ti,ab,kw. (31,909) 11 or/4–10 (62,185) 12 exp histamine H_2-receptor antagonist/(61,484) 13 exp ranitidine/(21,483) 14 exp cimetidine/(30,685) 15 exp famotidine/(7,264) 16 exp nizatidine/ (1,928) 17 ((histamine H_2 adj5 antagonist*) or H_2-receptor antagonist* or H_2RA or H_2RAs or H_2-RA or H_2-RAs or cimetidine or ranitidine or famotidine or nizatidine or roxatidine).ti,ab,kw. (23,645) 18 or/12–17 (63,515) 19 exp Helicobacter/ or exp *Helicobacter pylori*/ or exp Helicobacter infection/ (50,719) 20 (helicobacter or pylori or pyloridis or "HP" or Campylobacter).ti,ab,kw. (74,711)
	20 18 or 19 (62,395) 21 (test* adj3 (treat or manage* or therapy*)).ti,ab,kw. (10,129) 22 20 and 21 (369) 23 exp Endoscopy/(261,964) 24 (endoscop* or Gastroscop* or Duodenoscop*).ti,ab,kw. (59,007) 25 23 or 24 (286,034) 26 (initial adj3 (investigat* or manage* or procedure or strateg*)).ti,ab,kw. (9,656) 27 (empirical adj3 treat* or therap* or manage* or strateg*)).ti,ab,kw. (5,343) 28 10 or 17 or 22 or 25 or 26 or 27 (340,111) 29 3 and 28 (4,280) 30 randomized controlled trial.pt. (379,756) 31 controlled clinical trial.pt. (889,20) 32 random$.mp. (913,711) 33 placebo.ab. (156,611) 34 drug therapy.fs. (1,719,987) 35 trial.ab. (312,630) 36 groups.ab. (1,379,836) 37 or/30–36 (3,579,084) 38 29 and 37 (2,297) 39 exp animals/not humans/(3,972,902) 40 38 not 39 (2,292) 41 limit 40 to yr="2004 -Current" (955)	21 (test* adj3 (treat or manage* or therapy*)).ti,ab,kw. (13,763) 22 (19 or 20) and 21 (471) 23 exp endoscopy/ (413,319) 24 (endoscop* or Gastroscop* or Duodenoscop*).).ti,ab,kw. (88,994) 25 23 or 24 (436,324) 26 (initial adj3 (investigat* or manage* or procedure or strateg*)).ti,ab,kw. (12,734) 27 (empirical adj3 treat* or therap* or manage* or strateg*)).ti,ab,kw. (7,204) 28 11 or 18 or 22 or 25 or 26 or 27 (550,017) 29 3 and 28 (9,263) 30 random$.mp. (1,036,938) 31 double-blind:.mp. or placebo:.tw. or blind:.tw. (399,530) 32 30 or 31 (1,218,944) 33 29 and 32 (1,833) 34 exp animal/ not human/ (4,408,333) 35 33 not 34 (1,831) 36 limit 35 to yr="2004 -Current" (1,048)

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.

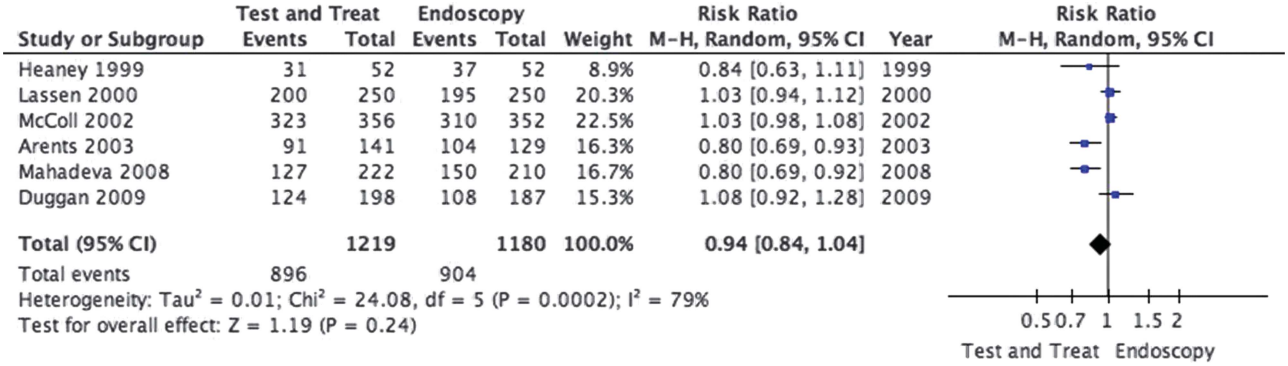

Figure 2. Forest plot of randomized controlled trials comparing *H. pylori* test and treat with early endoscopy with proportion having endoscopy as the outcome.

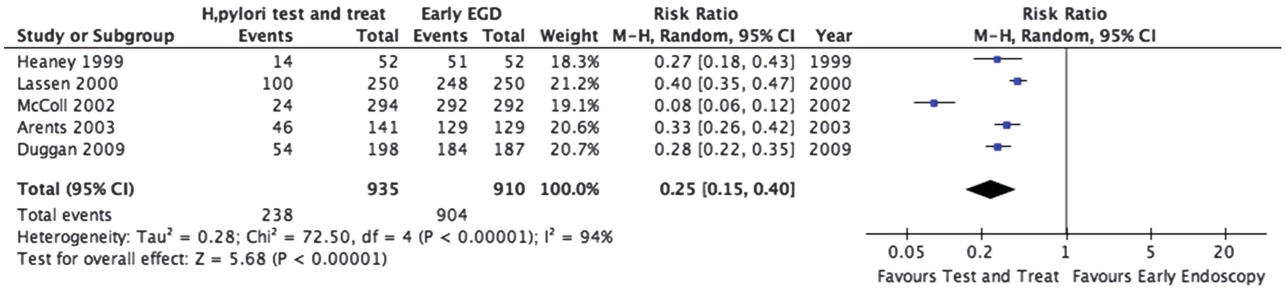

Figure 3. Forest plot of randomized controlled trials comparing *H. pylori* test and treat with early endoscopy with dyspepsia health service costs as the outcome.

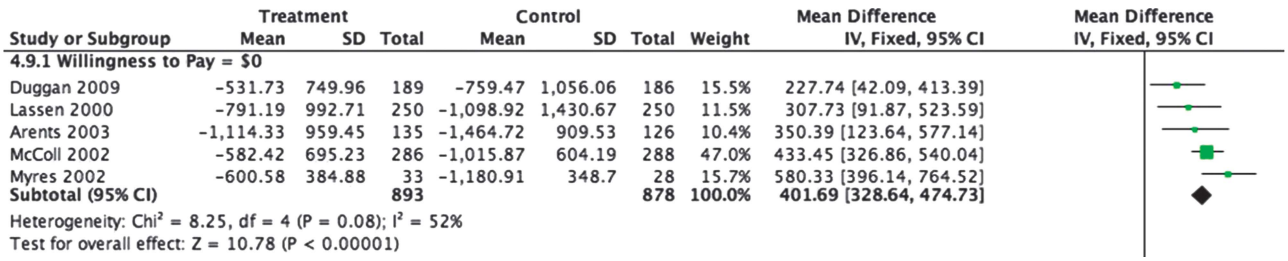

Figure 4. Forest plot of randomized controlled trials comparing *H. pylori* eradication with placebo antibiotics in infected dyspepsia patients.

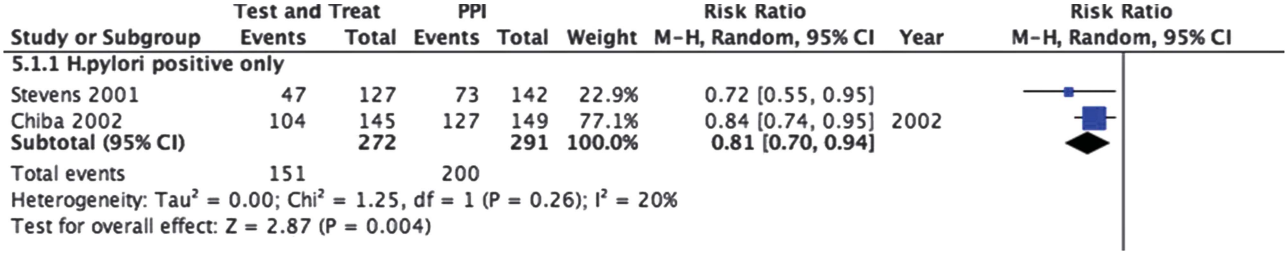

Figure 5. Forest plot of randomized controlled trials comparing *H. pylori* test and treat with empirical PPI therapy with continued dyspepsia as the outcome.

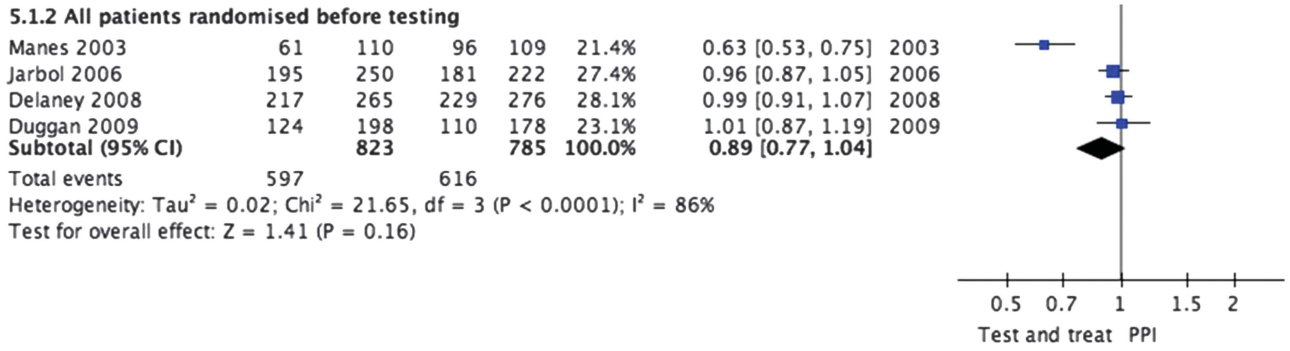

Figure 6. Forest plot of randomized controlled trials comparing empirical PPI therapy with placebo with continued dyspepsia as the outcome.

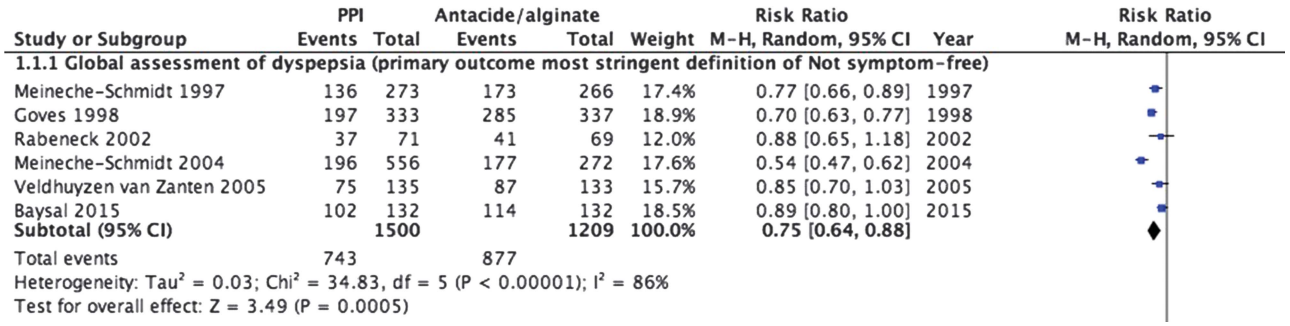

Figure 7. Forest plot of randomized controlled trials comparing empirical PPI therapy with H_2-receptor antagonists with continued dyspepsia as the outcome.

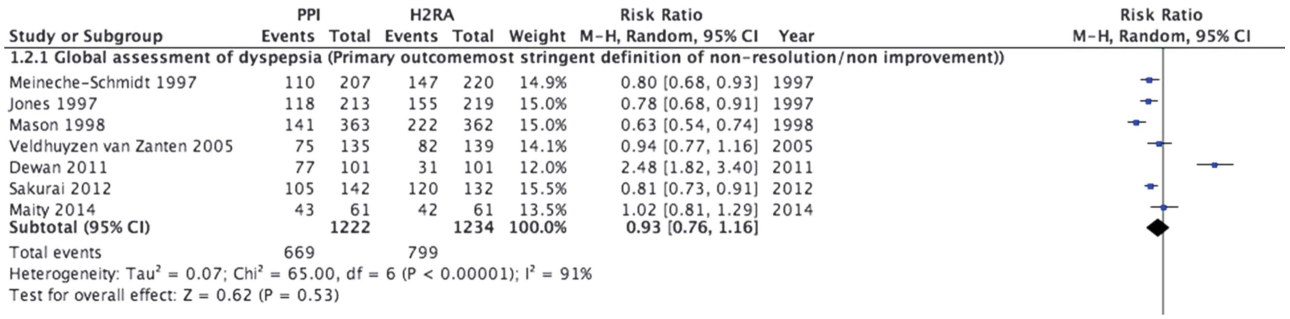

Figure 8. Forest plot of randomized controlled trials comparing empirical acid suppression therapy with early endoscopy with continued dyspepsia as the outcome.

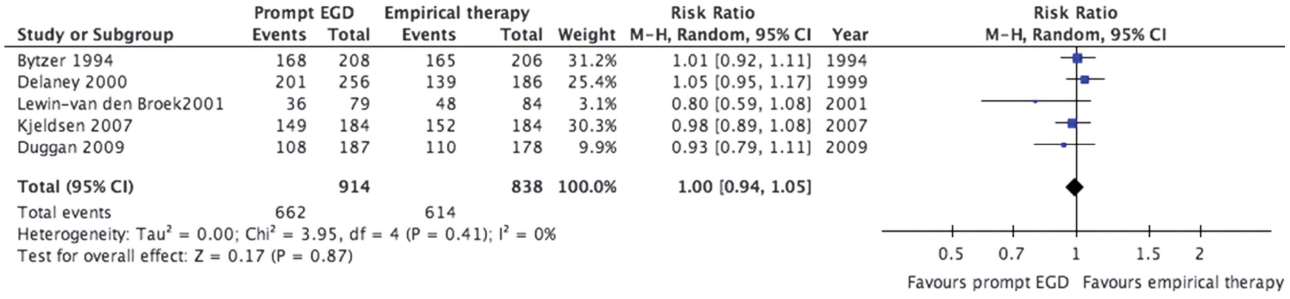

Figure 9. Forest plot of randomized controlled trials comparing empirical PPI therapy with prokinetic therapy with continued dyspepsia as the outcome.

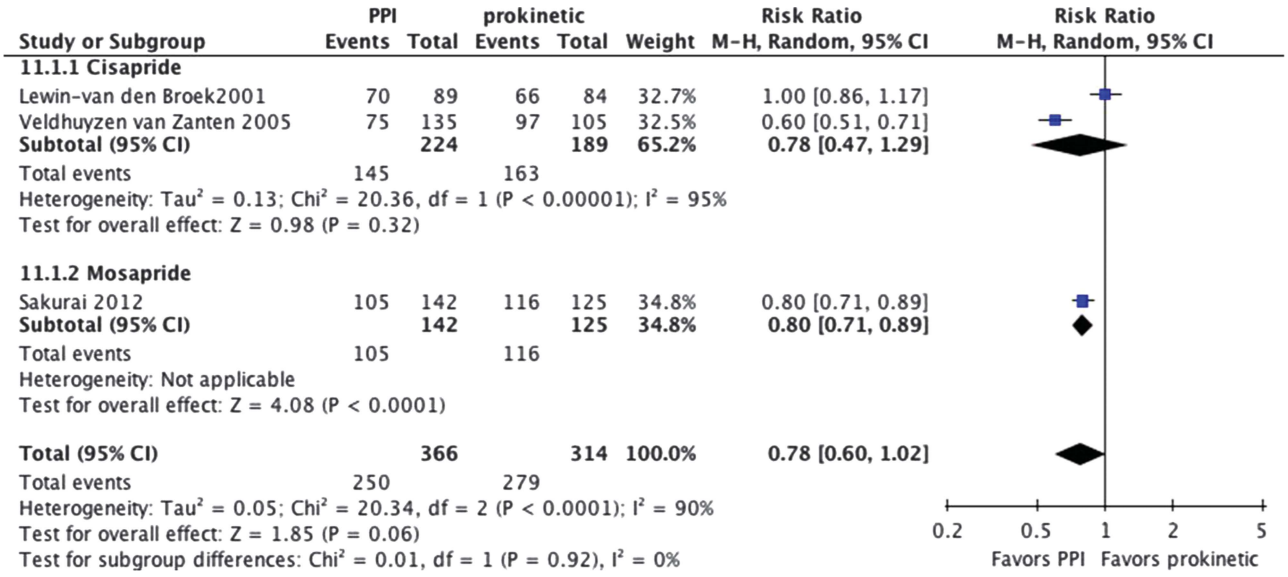

Figure 10. Forest plot of randomized controlled trials comparing *H. pylori* eradication with placebo antibiotics in *H. pylori*-infected patients with functional dyspepsia.

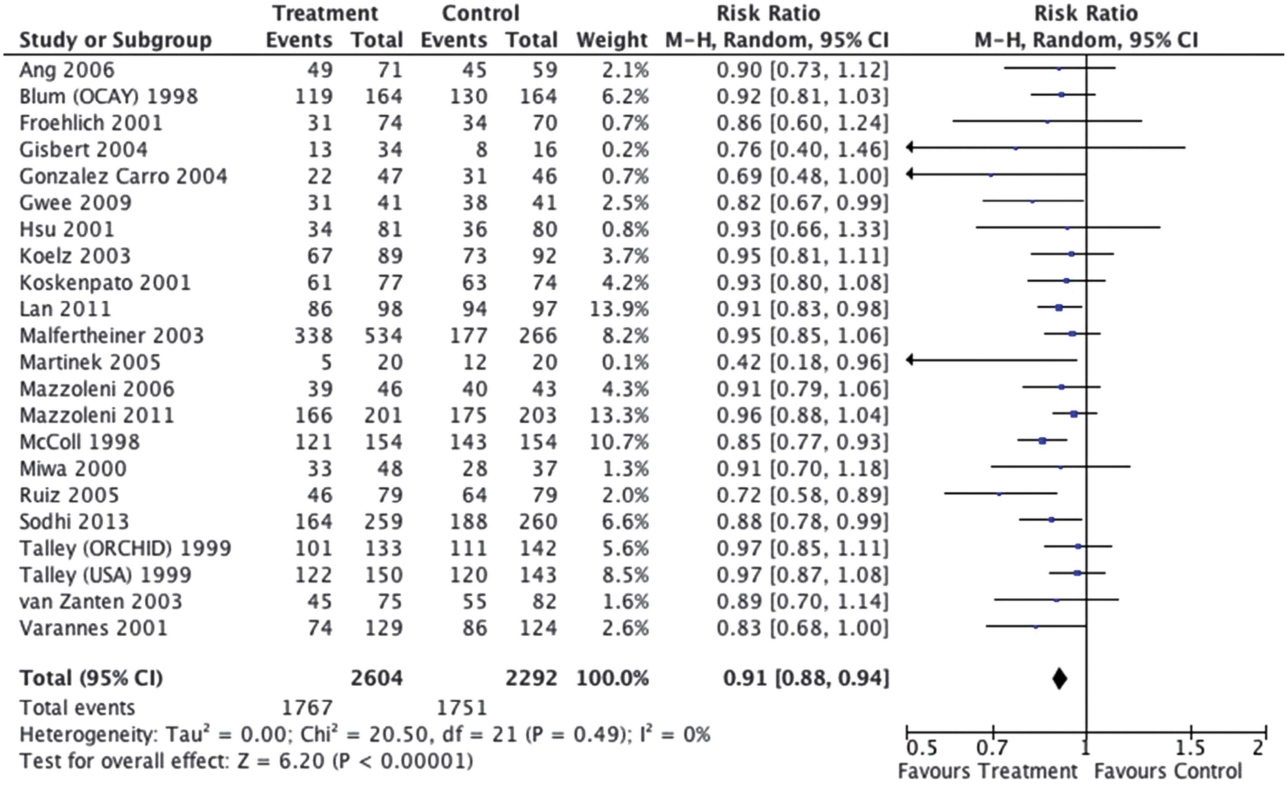

Figure 11. Forest plot of randomized controlled trials comparing proton pump inhibitors with placebo in functional dyspepsia patients.

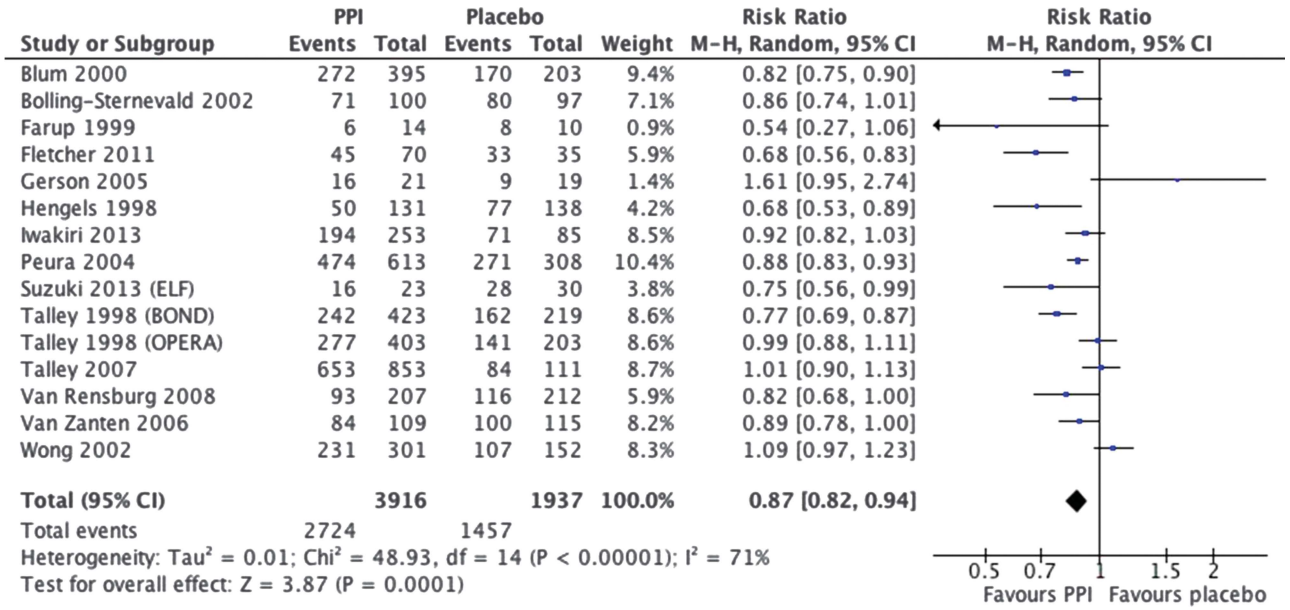

Figure 12. Forest plot of randomized controlled trials comparing proton pump inhibitors with prokinetics in functional dyspepsia patients.

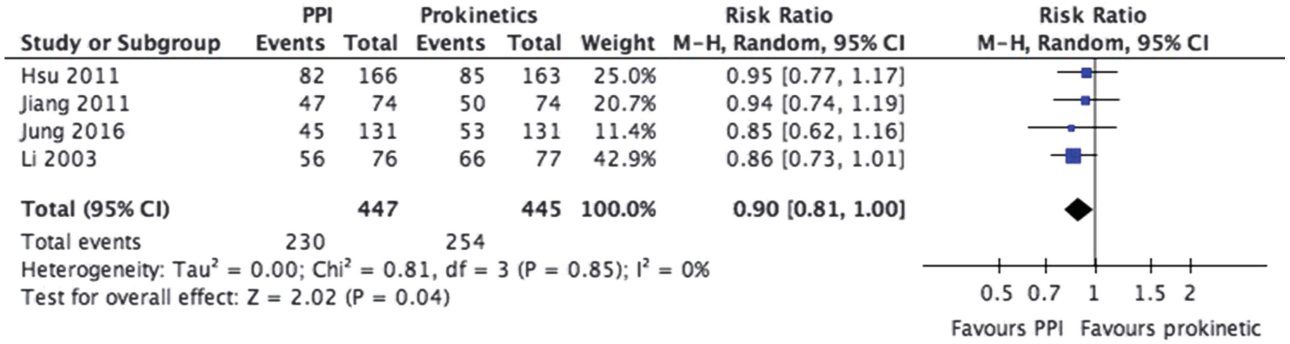

Figure 13. Forest plot of randomized controlled trials comparing motility modifying drugs with placebo in functional dyspepsia patients.

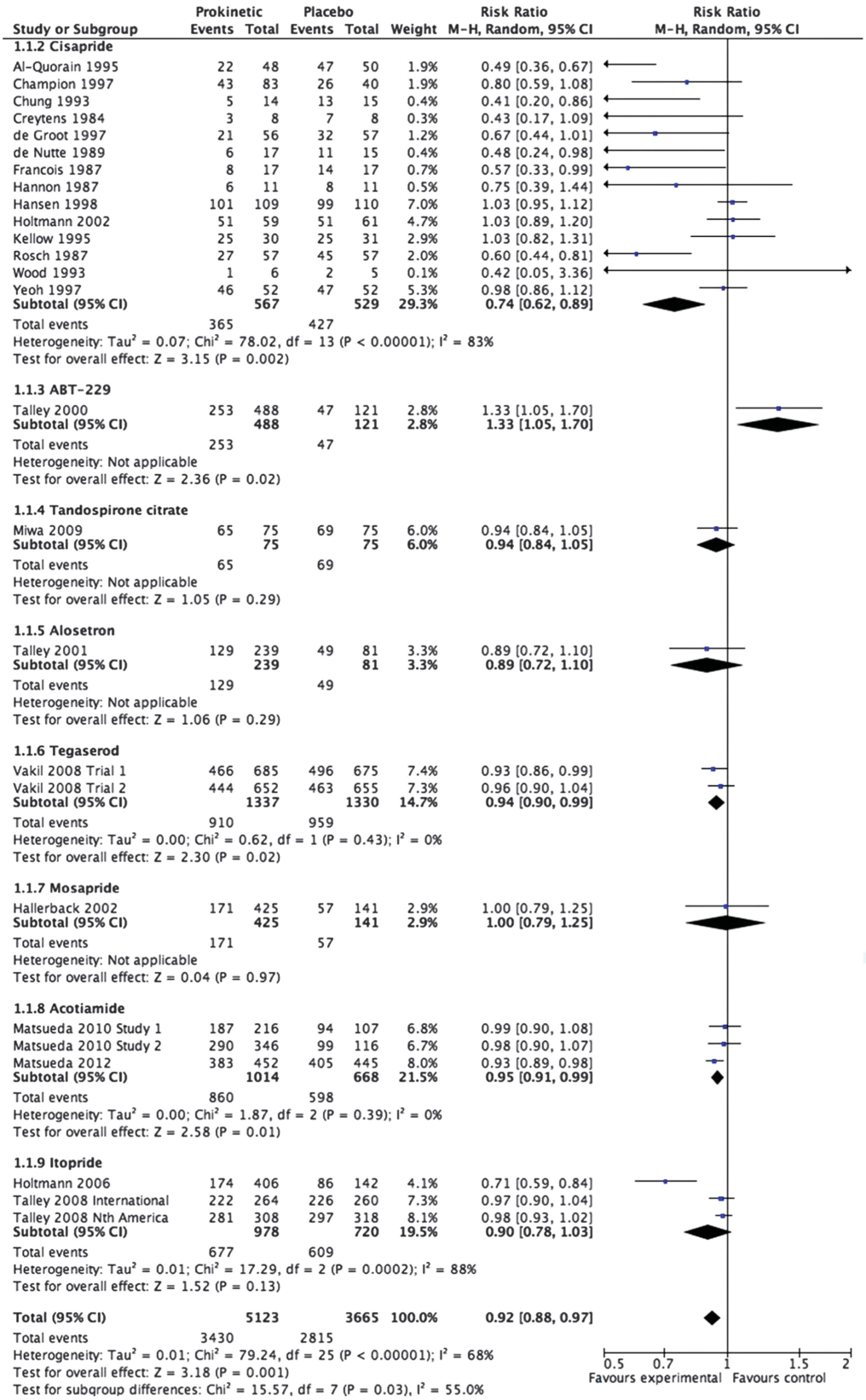

Figure 14. Forest plot of randomized controlled trials comparing domperidone with placebo in patients with upper GI symptoms.

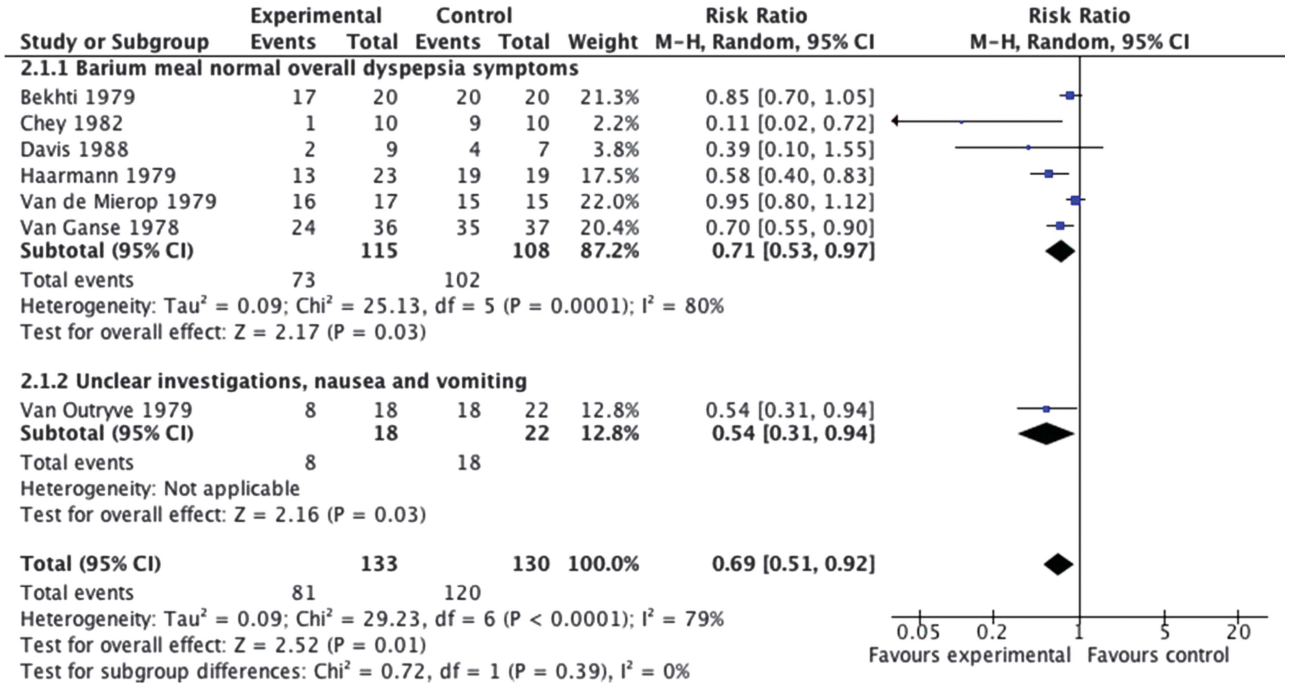

Figure 15. Forest plot of randomized controlled trials comparing psychological therapies with controls in functional dyspepsia patients.