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CLINICAL REVIEW

Dyspepsia

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Definitions of the term dyspepsia vary but generally describe pain or discomfort in the epigastric region. People with dyspepsia have a normal life expectancy,[1] but symptoms impair quality of life,[2 3] and affect productivity.[4] Dyspepsia is estimated to cost the United Kingdom more than £1bn (€1.16bn; $1.55bn) annually,[5] so it is important to manage the condition appropriately. We summarise recent systematic reviews, meta-analyses, and randomised controlled trials to provide the general reader with an update on how to deal with this disorder effectively.

What is dyspepsia and who gets it?

Dyspepsia is a symptomatic diagnosis. A variety of definitions have been proposed, but a reasonable working definition for the primary care doctor is epigastric pain or discomfort for at least three months, in a patient who does not report predominant heartburn or regurgitation (although these symptoms can be part of the overall symptom complex). Gastro-oesophageal reflux disease (GORD) becomes the more likely diagnosis if symptoms of heartburn or regurgitation predominate, although this is one of the main areas of contention surrounding the definition of dyspepsia. The condition is common worldwide, with 20-40% of the world's population affected,[6] depending on the definition used. Epidemiological surveys show no consistent association with sex, age, socioeconomic status, smoking, or alcohol use.[3 7]

Dyspepsia is more common in people who take non-steroidal anti-inflammatory drugs (NSAIDs) and drugs such as calcium antagonists, bisphosphonates, nitrates, and theophyllines. It is also more common in people infected with *Helicobacter pylori*.[7] A population based study also found an association between anxiety and dyspepsia symptoms,[8] and certain genetic polymorphisms are more prevalent in those with the condition.[9] There is a strong overlap between irritable bowel syndrome, gastro-oesophageal reflux symptoms, and dyspepsia,[10 11] suggesting that common genetic or environmental factors are involved in the development of these disorders.

What causes dyspepsia?

Several diseases can cause symptoms of dyspepsia. A systematic review identified nine studies (5389 participants) that performed endoscopy in a general population sample with dyspepsia.[12] Overall, there was a 13% prevalence of erosive oesophagitis and 8% prevalence of peptic ulcer disease, with gastric or oesophageal cancer occurring in less than 0.3% of endoscopies. Oesophagitis was more prevalent in Western populations than in Asian ones (25% *v* 3%), whereas the opposite was true for peptic ulcer disease (3% *v* 11%). Overall, 70-80% of people with dyspepsia had no clinically significant findings at endoscopy. Such patients are classed as having functional dyspepsia. The Rome III criteria for functional dyspepsia divide it into two separate syndromes. In epigastric pain syndrome, patients report intermittent pain or burning localised to the epigastric region. Patients with postprandial distress syndrome have bothersome postprandial fullness after an ordinary sized meal or early satiation that prevents a meal being finished.[13]

The pathophysiology of dyspepsia depends on the underlying disease. Peptic ulcer disease is usually caused by *H pylori* infection, with a few cases being associated with NSAIDs. GORD is caused by a combination of failure of the gastro-oesophageal junction to prevent acid reflux and impaired clearance of acid from the oesophagus. Although technically distinct from dyspepsia, it may present with dyspeptic-type symptoms, rather than heartburn or regurgitation.[14] Acid reflux may be severe enough to damage the oesophageal mucosa, in which case erosive oesophagitis will be visible at endoscopy.

Around 70-80% of patients with epigastric pain will have functional dyspepsia, and the causes of this disorder are poorly understood. Gastroduodenal dysmotility, and sensitivity to both distension and acid,[15] have all been proposed as possible causes. As well as peripheral mechanisms, there are changes in brain activity,[16 17] suggesting that central processing is also abnormal. Functional dyspepsia has therefore been described as multifactorial, which is probably why any individual treatment is effective only in a small proportion of patients.

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Summary points

Dyspepsia is common—about a fifth of people are affected at some point in their lives

The condition is chronic, with a relapsing and remitting nature

There is no evidence that dyspepsia adversely affects survival

In most patients, no cause for dyspepsia is detected at endoscopy

Gastro-oesophageal cancer is extremely rare in patients with dyspepsia who have no alarm symptoms

Most treatments are safe and well tolerated, but there is little evidence that they have any long term effect on the natural course of the disorder

Sources and selection criteria

We searched Medline, Embase, the Cochrane Database of Systematic Reviews, and Clinical Evidence online using the search term "dyspepsia", as well as recent conference proceedings. We limited studies to those conducted in adults and focused on systematic reviews, meta-analyses, and high quality randomised controlled trials published during the past five years whenever possible.

The causes of the central nervous system abnormalities, dysmotility, and hypersensitivity seen in functional dyspepsia are poorly understood. Several hypotheses have been proposed, including a subtle increase in inflammatory mediators in the upper gastrointestinal tract.[18] An observation that has garnered the most attention recently is the presence of eosinophils in the duodenum.[19] This has led to the hypothesis that the resulting increase in immune activation and inflammation may cause neuromodulation that gives rise to dysmotility, hypersensitivity, and central nervous system changes. The cause of this immune activation is uncertain, but it is most likely to be an infective process. The obvious candidate would be *H pylori* infection, but other infections can give rise to immune activation of the upper gastrointestinal tract. In support of this, it has been observed that dyspepsia is more common after an episode of acute gastroenteritis.[20]

How can the cause of dyspepsia be established?

Symptoms do not reliably distinguish between organic and functional disease,[21] and even alarm features (box), such as weight loss, are not particularly helpful.[22] Despite this, in the UK the presence of any of these alarm features is an indication for urgent specialist referral for endoscopy, to exclude upper gastrointestinal cancer.[23] Otherwise, endoscopy is not mandated in the management of dyspepsia, although it is the only way to accurately establish the underlying cause, including functional dyspepsia, which is a diagnosis of exclusion made in the absence of organic findings. However, no country can afford to perform endoscopy in all patients, and most guidelines recommend managing people under the age of 55 years with dyspepsia but no alarm features by testing for *H pylori* non-invasively with the urea breath test or stool antigen. Patients with positive results should be treated with eradication therapy and those with negative results given acid suppression therapy.[24] Gastric scintigraphy may help confirm delayed gastric emptying, particularly in patients with postprandial distress-type symptoms, to direct treatment, although the correlation between gastric emptying rates and symptoms is poor.[25]

What are the treatment options?

Uninvestigated dyspepsia in primary care or the community

An individual patient data meta-analysis of randomised controlled trials found that—although prompt endoscopy was superior to testing patients with uninvestigated dyspepsia for *H pylori*, and treating with eradication therapy if positive, in terms of symptom control at 12 months—it was not cost effective.[26] However, it is unclear whether a test and treat approach is preferable to empirical acid suppression first line, because a second individual patient data meta-analysis found no significant difference in symptoms or costs between the two.[27] Current guidelines state that either option can be used.[28] If the prevalence of *H pylori* in the population is known, it makes sense to use an acid suppression strategy first if prevalence is low (<10%) and an *H pylori* test and treat strategy if the prevalence is higher.[24] If these strategies are unsuccessful, other options (discussed below) can be considered, or the patient can be referred to secondary care for advice and further investigation if appropriate.

A six month primary care based Dutch trial compared two management strategies for uninvestigated dyspepsia based around empirical acid suppression.[29] One strategy used a step-up approach, starting with antacids, with treatment escalated to H_2 antihistamines and then proton pump inhibitors (PPIs) if symptoms remained uncontrolled. The second used a step-down approach, with the drugs given in the reverse order and de-escalated if symptoms improved. Treatment success (adequate relief of symptoms) was similar at six months (72% with step-up *v* 70% with step-down), but costs were significantly lower with the step-up approach. This, together with the small treatment effect in favour of step-up, meant that it came out top in a cost effectiveness analysis.

Another group of primary care patients who may benefit from *H pylori* test and treat are those who do not consult with dyspepsia very often but who require PPIs long term. A trial screened long term PPI users for *H pylori* and randomised those who were positive to eradication therapy or placebo.[30] Eradication therapy significantly reduced symptom scores, PPI prescriptions, consultations for dyspepsia, and dyspepsia related costs. The costs of detection and treatment were less than the money saved after two years of follow-up. Sensitivity analysis showed that the prevalence of *H pylori* would need to be less than 12% before this was no longer cost saving.

It has been estimated that 5% of dyspepsia in the community is attributable to *H pylori*,[7] so population screening and treatment for this organism could theoretically reduce dyspepsia related costs. Results from follow-up studies of people recruited to two large randomised controlled trials of population based screening (and eradication therapy or placebo if *H pylori* positive) in the UK suggest this might be the case, with significantly lower costs and fewer consultations after seven to 10 years.[31 32] However, these studies did not follow up all recruited people successfully, so currently there is insufficient evidence to institute population screening and treatment in the UK.

Upper gastrointestinal alarm symptoms (taken from National Institute for Health and Care (formerly Clinical) Excellence referral guidelines for suspected cancer[23])

- Age ≥55 years with new onset dyspepsia
- Chronic gastrointestinal bleeding
- Dysphagia
- Progressive unintentional weight loss
- Persistent vomiting
- Iron deficiency anaemia
- Epigastric mass
- Suspicious barium meal result

Peptic ulcer disease

The causal role of *H pylori* in peptic ulcer disease is well established, and patients with *H pylori* positive disease should receive eradication therapy. A Cochrane review found that the number needed to treat (NNT) with eradication therapy to prevent one duodenal ulcer relapse (26 placebo controlled trials) was 2 and for gastric ulcer (nine trials) the number was 3.[33] Although there was significant heterogeneity between studies in both analyses, all but one trial showed a significant benefit with eradication therapy. PPI triple therapy (a PPI plus two antibiotics (clarithromycin with amoxicillin or metronidazole)) should be used in areas like the UK where clarithromycin resistance is less than 10%, with bismuth quadruple therapy (bismuth plus a PPI and two antibiotics) being given where resistance is higher.[34] Most cases of *H pylori* negative peptic ulcer disease are caused by NSAIDs, and trials show that PPIs are superior to H_2 antihistamines for ulcer healing in this situation.[35 36] *H pylori* negative, NSAID negative peptic ulcer disease is rare and probably requires long term PPI treatment.

Functional dyspepsia

Diet and lifestyle

Food diaries from a small study of 29 patients suggest that people with functional dyspepsia eat fewer meals and consume less energy and fat than healthy controls,[37] but whether this is a cause or a consequence of symptoms is unclear. Although the prevalence of undiagnosed coeliac disease is higher in people with symptoms of irritable bowel syndrome,[38] this is not the case in dyspepsia.[39] It is also unclear whether non-coeliac gluten sensitivity is involved in symptom generation in some patients with functional dyspepsia. Doctors often advise people with dyspepsia to lose weight, avoid fatty food and alcohol, or stop smoking, but there is little evidence that these measures improve symptoms.[40] As a result, drugs are the mainstay of treatment.

Acid suppression therapy

Antacids neutralise gastric acid, the production of which is controlled by gastrin, histamine, and acetylcholine receptors. Once stimulated, these receptors activate proton pumps in the parietal cell. H_2 antihistamines and PPIs reduce acid production by blocking H_2 receptors or the proton pump, respectively. Because PPIs act on the proton pump itself, these drugs lead to more profound acid suppression than H_2 antihistamines or antacids.

A Cochrane review has studied the efficacy of acid suppressants in functional dyspepsia.[41] One placebo controlled trial of antacids showed no benefit. Twelve randomised controlled trials of H_2 antihistamines versus placebo found that these drugs were effective for the treatment of functional dyspepsia (NNT=7). However, there was significant heterogeneity between studies, which was not explained by sensitivity analysis, and evidence of funnel plot asymmetry, suggesting publication bias or other small study effects. Their efficacy may therefore have been overestimated. Ten trials studied PPIs. Again, there was a significant benefit over placebo, although this was modest (NNT=10). There was significant heterogeneity between studies, with no obvious explanation, but no funnel plot asymmetry. A subgroup analysis conducted according to predominant symptom showed that PPIs were most beneficial in patients with reflux-type symptoms and more effective than placebo in patients with epigastric pain. However, they were no more effective than placebo in those with dysmotility-like functional dyspepsia.[42]

Most trials used PPIs for four to eight weeks. This seems a reasonable duration, especially as concerns have been raised recently about the safety of long term PPI use. Observational studies suggest that hip fracture, community acquired pneumonia, and *Clostridium difficile* infection are more common in PPI users,[43 44] although all these associations were extremely modest, and direct causation cannot be assumed from studies such as these.

H pylori eradication therapy

The benefit of eradication therapy is less pronounced in functional dyspepsia than in peptic ulcer disease, but treatment is still more effective than placebo. In a Cochrane review of 21 placebo controlled trials the NNT for improvement in symptoms after eradicating *H pylori* was 14, with no heterogeneity between studies and no evidence of funnel plot asymmetry.[45]

Prokinetic drugs

Prokinetics enhance gastrointestinal motility. Examples include 5-hydroxytryptamine-4 (5-HT_4) receptor agonists, such as cispride and mosapride, and the dopamine antagonists metoclopramide and domperidone. A Cochrane review identified 24 placebo controlled trials of prokinetics in functional dyspepsia.[41] Most used cisapride, which has been withdrawn owing to concerns over cardiac safety, with only one trial studying mosapride or domperidone, and no randomised controlled trials of metoclopramide. Overall, these drugs seemed to be highly effective (NNT=6). However, there was significant heterogeneity between studies, which was not explained by sensitivity analysis, and funnel plot asymmetry, which suggests that their apparent efficacy may be due to publication bias. In addition, when only high quality trials were included in the analysis the benefit was no longer apparent.[46]

Antidepressants and psychological therapies

Patients with functional dyspepsia, as with most other functional gastrointestinal disorders, have higher rates of anxiety, depression, and other psychological conditions than healthy people.[47] Antidepressants seem to be of benefit in irritable bowel

syndrome,[48] and three trials have recently been conducted in functional dyspepsia. In a Chinese study, a low dose of the tricyclic antidepressant imipramine was significantly more effective than placebo (response rate 64% *v* 44%).[49] In another Chinese trial the selective serotonin reuptake inhibitor sertraline was not superior to placebo (28% experienced complete symptom resolution in both treatment arms).[50] Finally, in a placebo controlled trial of the tricyclic antidepressant amitriptyline or the selective serotonin reuptake inhibitor escitalopram, only amitriptyline showed a significant benefit over placebo.[51] Withdrawal owing to adverse events was more common with antidepressants in all three trials. These findings suggest that, if an antidepressant is used, a tricyclic is preferable.

A Cochrane review of the efficacy of psychological interventions in functional dyspepsia identified four trials.[52] Formal meta-analysis was not possible because of incomplete data reporting. The authors concluded that insufficient evidence existed for any benefit. Little has been published since this systematic review. A small randomised controlled trial of patients in whom conventional treatments had failed compared cognitive behavioural therapy (CBT) as an adjunct to intensive medical treatment (including testing for and targeting motor and sensory abnormalities) with intensive medical treatment alone or standard medical treatment.[53] A response was significantly more likely with intensive medical therapy combined with CBT compared with standard treatment (54% *v* 17%), but response rates were similar with intensive medical treatment alone (46%), suggesting that CBT may have no additive benefit. Despite the lack of evidence for any benefit, it seems reasonable to consider psychological treatments in patients with troublesome symptoms who have coexistent anxiety or depression.

Alternative therapies

In a randomised controlled trial that compared acupuncture with a sham procedure in functional dyspepsia, response rates were significantly higher with true acupuncture (71% *v* 35%).[54] A smaller sham controlled trial,[55] which included neurological imaging studies, found that acupuncture led to deactivation of the anterior cingulate cortex, insula, thalamus, and hypothalamus, which are all involved in processing painful visceral stimuli, perhaps explaining its therapeutic mechanism.

The herbal preparation iberogast, also known as STW5, which is a combination of plant extracts, has been tested in several trials of functional dyspepsia. Iberogast significantly improved symptom scores compared with placebo in one trial,[56] and in another 43% of patients randomised to iberogast reported resolution of symptoms at eight weeks compared with only 3% with placebo.[57] A single placebo controlled trial also found that peppermint oil, combined with caraway oil, was beneficial in functional dyspepsia.[58] At the time of writing, no randomised controlled trials have investigated probiotics in dyspepsia.

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Tips for non-specialists

- Treat peptic ulcer disease with eradication therapy if *Helicobacter pylori* is present or proton pump inhibitors if non-steroidal anti-inflammatory drugs are implicated
- Eradication therapy may be beneficial in *H pylori* positive functional dyspepsia, although the effect is modest
- Proton pump inhibitors, H_2 antihistamines, and prokinetics may be beneficial in *H pylori* negative functional dyspepsia or in patients who do not benefit from eradication therapy
- Proton pump inhibitors are beneficial in patients with functional dyspepsia who mainly have reflux symptoms or epigastric pain, but not in those with dysmotility-like symptoms
- Increasing evidence suggests that tricyclic antidepressants, but not selective serotonin reuptake inhibitors, are beneficial in functional dyspepsia
- There is no evidence that psychological treatments are of benefit in functional dyspepsia
- Alternative therapies should be reserved for patients with functional dyspepsia whose symptoms are not relieved by conventional treatments

Additional educational resources box

Resources for healthcare professionals

- Leontiadis GI, Moayyedi P, Ford AC. Helicobacter pylori infection. *Clin Evid (Online)* 2009;pii:0406. An up-to-date summary of the evidence for the eradication of *Helicobacter pylori* in various situations
- National Institute for Clinical Excellence. Dyspepsia. Managing dyspepsia in adults in primary care. www.nice.org.uk/nicemedia/live/10950/29460/29460.pdf . NICE clinical guideline

Resources for patients

- Patient.co.uk (www.patient.co.uk/health/dyspepsia-indigestion)—Patient information on dyspepsia (indigestion)
- NHS Choices (www.nhs.uk/Conditions/Indigestion/Pages/Introduction.aspx)—Information from the NHS on indigestion

Questions for future research

- Are psychological treatments of benefit in functional dyspepsia?
- Does dietary manipulation have a role to play in the management of functional dyspepsia?
- Is non-coeliac gluten sensitivity implicated in symptom generation in a proportion of patients with presumed functional dyspepsia?

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