Investigation and management of functional dyspepsia

Dyspepsia is a common presentation but only a small minority of patients have organic pathology. The majority have functional dyspepsia. All physicians should have a framework to manage dyspepsia to avoid over-investigation but to also recognize when it is appropriate to refer patients for further investigations.

Dyspepsia is a heterogeneous group of abdominal symptoms that can cause significant morbidity, resulting in substantial costs to the health service. When there is no organic cause identified for these symptoms this is termed as functional dyspepsia.

Functional dyspepsia can be defined by the Rome III diagnostic criteria (Rome Foundation, 2006). These state that, to fulfil the criteria for functional dyspepsia, one or more of the following must be present:

- Bothersome postprandial fullness
- Early satiation
- Epigastric pain
- Epigastric burning.

The symptoms must have been present for at least 3 months with symptom onset at least 6 months before the diagnosis and there must be no evidence of structural disease that is likely to explain the symptoms. Heartburn is excluded from the diagnostic criteria as this is thought to originate in the oesophagus and is more suggestive of gastro-oesophageal reflux disease, although functional dyspepsia and gastro-oesophageal reflux disease can occur concomitantly. There is a large overlap between functional dyspepsia, gastro-oesophageal reflux disease and irritable bowel syndrome.

Epidemiology and causes

The prevalence of dyspepsia is approximately 40% (Scottish Intercollegiate Guidelines Network, 2003) and is the main presenting complaint in 5% of all consultations every year. Each year 3% of the population take treatments for dyspepsia at a cost of £500 million and approximately 450 000 endoscopies each year are performed to investigate dyspepsia (Delaney et al, 2008). The causes of dyspepsia are outlined in *Table 1*.

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Around 50% of patients with dyspepsia have functional dyspepsia and of those that do undergo endoscopy, approximately 40% have functional dyspepsia, 40% have gastro-oesophageal reflux disease, 13% have peptic ulcer disease and around 3% have oesophageal or gastric malignancy (National Institute for Health and Clinical Excellence, 2004). Other less common causes include hepatobiliary disease, pancreatic disease, irritable bowel syndrome and metabolic disorders such as hypercalcaemia.

Who should be referred for upper gastrointestinal endoscopy?

Endoscopic investigation of all patients with dyspepsia is not affordable and National Institute for Health and Clinical Excellence (2004) guidance states that there is no indication for endoscopic investigation in dyspeptic patients under the age of 55 years who do not have any red flag symptoms or signs. In all patients over the age of 55 years, the National Institute for Health and Clinical Excellence (2004) recommends urgent referral (less than 2-week wait) with unexplained, persistent new-onset dyspepsia.

Red flag signs and symptoms that require urgent referral for upper gastrointestinal endoscopy for patients of any age are shown in *Table 2* (National Institute for Health and Clinical Excellence, 2005).

Management of uninvestigated dyspepsia

The majority of patients do not require endoscopic investigation of dyspepsia and physicians should have a framework for managing symptoms in these patients.

Lifestyle advice

All patients should be offered lifestyle advice although the evidence that this makes a difference to dyspepsia

Table 1. Causes of dyspepsia

Functional
Gastro-oesophageal reflux (erosive and non-erosive)
Medication-induced
Peptic ulcer disease
Malignancy

symptoms is weak (National Institute for Health and Clinical Excellence, 2004). In particular there is no clear association between dyspepsia and lifestyle factors such as caffeine, alcohol, chocolate, smoking and stress. However, each case should be treated individually and patients should learn to recognize precipitants that make their symptoms worse. Other measures include weight reduction, introduction of smaller and more frequent meals as well propping up the head end of the bed if symptoms are particularly bothersome at night.

Medication review

A number of medications are known to cause dyspepsia. All over-the-counter and prescribed medications should be reviewed to see if they are a potential cause of dyspepsia. The most common offending drugs are listed in *Table 3*.

Dyspepsia symptoms can also be avoided or reduced if patients are adequately counselled before commencing a medication. For example, bisphosphonates should be taken 30 minutes before food or other medication, while sitting upright and with plenty of water. The patient should remain upright for at least 30 minutes after taking the drug. In addition, when prescribing or recommending a drug known to cause dyspepsia, such as a non-steroidal anti-inflammatory drug, consider offering a concomitant prescription of a proton-pump inhibitor or H_2-receptor antagonist to patients at high risk. High-risk patients include the elderly, those already on other drugs that might irritate the stomach and those with a past history of peptic ulceration.

Table 2. Criteria for urgent referral for upper gastrointestinal endoscopy for patients of any age

Dysphagia
Progressive unintentional weight loss
Persistent vomiting
Iron deficiency anaemia
Chronic gastrointestinal bleeding
Epigastric mass
Suspicious barium meal

Table 3. Causes of medication-induced dyspepsia

Non-steroidal anti-inflammatory drugs
Aspirin
Bisphosphonates
Corticosteroids
Antibiotics
Selective serotonin-reuptake inhibitors
Iron preparations
Calcium antagonists
Nitrates
Theophylline

The role of *Helicobacter pylori* in functional dyspepsia

Several studies have shown only a modest improvement in dyspeptic symptoms following eradication of *Helicobacter pylori,* with a number needed to treat of approximately 17 in one Cochrane review (Moayyedi et al, 2004). This is similar to the number needed to treat for empirical treatment with proton-pump inhibitors.

However, studies have shown that the 'test and treat' approach for *H. pylori* does lead to a reduction in the number of endoscopies performed and is equally cost effective as empirical treatment with proton-pump inhibitors in the first instance (Delaney et al, 2008). Both the American Gastroenterology Association (Talley, 2005) and Scottish Intercollegiate Guidelines Network (2003) advocate the 'test and treat' approach and then empirical treatment with proton-pump inhibitors if symptoms persist. National Institute for Health and Clinical Excellence has no clear preference for whether or not 'test and treat' for *H. pylori* should be before or as a result of failure of empirical proton-pump inhibitor treatment.

H. pylori can be tested using a carbon-13 (C-13) urea breath test, a stool antigen test or serology. Carbon-13 urea breath test and stool antigen test are accurate tests with sensitivity and specificity of 92–95%. Serological testing of immunoglobulin antibodies in the blood against *H. pylori* has a sensitivity of 92% but a specificity of only 83% (Scottish Intercollegiate Guidelines Network, 2003). Antibodies can persist for *H. pylori* even after eradication, making interpretation difficult if there is a need to retest. Irrespective of the method used it is essential that proton-pump inhibitors are stopped for at least 2 weeks before testing in order to reduce the likelihood of a false negative result.

The two most commonly prescribed eradication treatments are PAC500 (proton-pump inhibitor, amoxicillin 1 g twice daily and clarithromycin 500 mg twice daily) and PMC250 (proton-pump inhibitor, metronidazole 400 mg twice daily and clarithromycin 250 mg twice daily). Resistance to both clarithromycin and metronidazole is common and can develop during treatment, and *H. pylori* eradication is successful in approximately 80–85% of patients, which means that treatment fails to eradicate *H. pylori* in approximately one in five patients (National Institute for Health and Clinical Excellence, 2004).

There is no role for retesting for *H. pylori* after eradication unless there is no response to or a relapse of symptoms (National Institute for Health and Clinical Excellence, 2004). A 2-week regimen comprising a pro-

ton-pump inhibitor, tripotassium dicitratobismuthate 120 mg four times daily, tetracycline 500 mg four times daily and metronidazole 400–500 mg three times daily can be used in the event of eradication failure.

Pharmacological treatment

Antacids and alginates

Antacids are often used as first line in the management of dyspepsia. They are usually magnesium or aluminium based and less commonly calcium based. They are used at the time of symptoms or if they are expected, usually after meals and/or bedtime. Alginates can be used in combination with antacids and are usually a combination of sodium alginate, sodium bicarbonate and calcium carbonate. They work by increasing the viscosity of gastric contents and provide a protective layer for the oesophagus from reflux.

Proton-pump inhibitor and H_2-receptor antagonist therapy

Once a decision has been taken to commence a proton-pump inhibitor this should be offered as a 1-month trial of full-dose proton-pump inhibitor therapy. Proton-pump inhibitors should be used in preference to H_2-receptor antagonists as they are better at controlling symptoms, with an average response rate of 58% and 36% for proton-pump inhibitor and H_2-receptor antagonist therapy respectively (National Institute for Health and Clinical Excellence, 2004).

If the decision is taken to continue proton-pump inhibitor therapy as part of a long-term management strategy than physicians should review the continued need for this medication at regular intervals and should step the patient down to the lowest dose required to control symptoms.

There is increasing evidence of long-term side effects associated with proton-pump inhibitor therapy, including increased risk of enteric infections such as *Clostridium difficile* and an association with electrolyte disturbances such as hypomagnesaemia. There is also thought to be a possible association between long-term proton-pump inhibitor therapy and reduced bone mineral density, although studies have produced conflicting results (Abraham, 2012).

Prokinetics

If symptom control is not achieved with proton-pump inhibitors then prokinetics such as metoclopramide or domperidone should be considered. They can be used in combination with proton-pump inhibitors when these alone have not been effective. Metoclopramide is able to cross the blood–brain barrier and is therefore limited by its side-effect profile which can include Parkinsonism-type signs and symptoms, tardive dyskinesia and hyperprolactinaemia. Domperidone has a better side-effect profile than metoclopramide as it does not cross the blood–brain barrier. The evidence for the effectiveness of prokinetics in the management of functional dyspepsia is limited although they are probably better than placebo and are likely to be most effective in symptoms that develop after meals (McNally and Talley, 2007).

Antidepressants and alternative therapies

The evidence for the efficacy of antidepressants in functional dyspepsia is limited although tricyclic antidepressants have been used successfully in other functional disorders such as irritable bowel syndrome (Moayyedi, 2012).

Alternative therapies have yielded mixed results. In one randomized control trial, hypnotherapy was shown to be effective for both short- and long-term improvement in symptoms and quality of life (Hamilton et al, 2000). Cognitive behavioural therapy and psychotherapy have been shown to reduce dyspeptic symptoms although a Cochrane review concluded that there was insufficient evidence to recommend these treatments in the long-term management of functional dyspepsia (Soo et al, 2005).

Long-term management

All patients should be reviewed at least on an annual basis to address their ongoing management. If possible patients should be encouraged to take control of their own management. This should include adjusting their medication in a stepwise manner to ensure symptoms are controlled on the lowest dose treatment and being encouraged to use their medication on an 'as required' basis. Lastly, patients should be reassured of the benign nature of their disease in order to avoid unnecessary anxiety and over-investigation.

KEY POINTS

- Dyspepsia is a common presenting symptom but only a small proportion of patients will have any significant pathology. Endoscopic investigation in all patients presenting with dyspepsia is not feasible or recommended.
- Any patient presenting with alarm symptoms and patients over the age of 55 years with persistent and recent-onset dyspepsia alone should be referred for an urgent upper gastrointestinal endoscopy.
- The role of *Helicobacter pylori* in functional dyspepsia remains controversial but a 'test and treat' approach for *H. pylori* seems sensible as a first management step.
- Managing dyspepsia should include a medication review, lifestyle adjustments, use of antacids and alginates as well as other pharmacotherapy including proton-pump inhibitors, histamine type-2 receptor antagonists and prokinetics.
- Further research into the efficacy of antidepressants and alternative treatments such as hypnotherapy and psychotherapy is needed.

Continued on p. 211

Continued from p. 210

Conclusions

The majority of patients presenting with dyspepsia will have functional dyspepsia. In those that do not meet the criteria for urgent upper gastrointestinal endoscopy, it is reasonable to offer a 'test and treat' approach for *H. pylori* and/or empirical treatment with a proton-pump inhibitor. Lifestyle measures should be addressed and a medication review is always essential. Pharmacological treatment should be individually tailored and alternative therapies may need to be explored in those that do not have adequate symptom control. **BJHM**

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