Dyspepsia is a frequent symptom, with prevalence estimated between 19 and 41 per cent from a recent meta-analysis in Europe. It accounts for approximately 2–5 per cent of all visits to GPs. Prescribed drugs and endoscopies currently cost the NHS £600 million annually.

This article aims to elucidate some of the finer aspects of dyspepsia, highlight common pitfalls and touch on elements of pharmacology, as a better understanding of this will help rationalise drug prescribing. We also outline new therapies that are on the horizon.

**Defining dyspepsia**

The definition of dyspepsia (as well as functional dyspepsia) has evolved over time. The most recent consensus committee, Rome III, has defined dyspepsia as ‘the presence of symptoms considered by the physician to originate from the gastroduodenal region’.

The four symptoms that are considered specific for this are: bothersome postprandial fullness, early satiation, epigastric pain and epigastric burning. Less specific symptoms that may be associated are: bloating, nausea, vomiting and belching. The committee also decided that when heartburn is the predominant symptom the patient should be considered to have gastro-oesophageal reflux disease (GORD) and not dyspepsia. In reality, these patients present with multiple symptoms to their GP that overlap with other functional gastrointestinal disorders, including irritable bowel syndrome.

The term functional dyspepsia is gaining considerable attention and efforts to understand its pathophysiology and possible treatments are underway. It is defined as the presence of early satiation, postprandial fullness, epigastric pain and burning in the absence of organic, systemic or metabolic disease. Two particular
subgroups are identified: postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS). 2

Causes
The main causes of dyspepsia based on endoscopy findings are shown in Figure 1. A more comprehensive list of causes is shown in Table 1. 3 The important identifiable causes are peptic ulcer disease, GORD and nonulcer/functional dyspepsia; while malignancy is important to exclude it is relatively less common.

Pitfalls to avoid are missing diagnoses of acute myocardial ischaemia, early pregnancy, medication-induced dyspepsia and mesenteric ischaemia. The key to this is obtaining a detailed and focused history and reviewing the patient’s medications.

Investigation and management
NICE guidelines (2004, updated in 2005) are available to guide further assessment and referral, 4 and this has also been addressed in a previous Prescriber article in 2010. 5 The overall management of dyspepsia has not changed significantly since then, and this section is adapted to highlight key points of the guidelines.

The main priority is identifying alarm signals that trigger a referral to endoscopy (see Table 2). The NICE guideline differentiates between uninvestigated and investigated dyspepsia, i.e. referred for endoscopy. In the investigated dyspepsia group, management then depends on the three main categories: GORD, peptic ulcer disease or nonulcer dyspepsia/functional dyspepsia.

Figures 2 and 3 illustrate useful algorithms for assessing and managing uninvestigated and investi-

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<tr>
<th>Luminal GI tract</th>
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<tr>
<td>chronic gastric volvulus, chronic gastric/intestinal ischaemia, food intolerance, functional dyspepsia, GORD, gastric/oesophageal neoplasms, gastric infections, gastroparesis, infiltrative/inflammatory disorder (Crohn’s, sarcoidosis), irritable bowel syndrome, Ménétrier’s disease, peptic ulcer disease, parasites (Giardia, Strongyloides)</td>
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<th>Medications</th>
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<td>acarbose, aspirin, bisphosphonates, calcium channel blockers, NSAIDs, colchicine, digitalis, oestrogens, ethanol, gemfibrozil, glucocorticoids, iron, levodopa, niacin, narcotics, nitrates, orlistat, potassium chloride, quinidine, sildenafl, theophylline</td>
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<th>Pancreaticobiliary disorders</th>
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<td>biliary pain – cholelithiasis, choledocholithiasis, sphincter of Oddi dysfunction, chronic pancreatitis, pancreatic neoplasms</td>
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<th>Systemic conditions</th>
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<td>adrenal insufficiency, congestive heart failure, diabetes mellitus, hyperparathyroidism, intra-abdominal non-gastrointestinal malignancy, MI, pregnancy, renal insufficiency, thyroid disease</td>
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Table 1. Causes of dyspepsia

Uninvestigated dyspepsia
There are two strategies offered: test and treat for Helicobacter pylori or empirical treatment with a proton pump inhibitor (PPI). There is currently insufficient evidence to guide which should be offered first.

Investigated dyspepsia
For GORD, offer full-dose PPI for one or two months. In peptic ulcer disease, test and treat for H. pylori. Stop use of NSAIDS where possible. Gastric ulcers should be followed up with a repeat endoscopy in six to eight weeks. In nonulcer dyspepsia/functional dyspepsia, test and treat for H. pylori. If H. pylori negative treat with low-dose PPI for one month.

Refractory cases
Additional investigations may be pursued (usually in a secondary setting) for patients with refractory dyspepsia. Testing for coeliac disease and Giardia infection is useful. Abdominal ultrasound can be used to rule out pancreaticobiliary disease. Gastric emptying
studies using scintigraphy can evaluate severe post-prandial fullness. Oesophageal pH with impedance monitoring can be used to diagnose atypical presentations of GORD.

**Treatment**

The current evidence base for efficacy of lifestyle and dietary measures in dyspepsia has not changed significantly over the years. Advising patients to eat more-frequent smaller meals seems sensible. Cessation of smoking and alcohol consumption is recommended but without convincing evidence that this truly works.

Dyspepsia due to underlying structural disease such as peptic ulcer disease or GORD should be treated accordingly. Treatment options for functional dyspepsia are limited but the mainstay of pharmacotherapy for this condition consists of prokinetic agents, PPIs and H₂-antagonists. In a systematic review these drugs were shown to be more effective than placebo. There was no statistically significant benefit from antacids, bismuth chelate (tripotassium dicitratobismuthate, De-NolTab) or sucralfate (Antepsin). PPIs have demonstrated superior efficacy compared with H₂-antagonists due to maintenance of intragastric pH >4 for more sustained periods following administration.

To optimise the efficacy of our current arsenal of therapeutics one should pay heed to their mechanism of action, particularly the PPIs. The PPIs are most effective when the gastric parietal cell is stimulated to secrete acid postprandially; therefore, PPIs should be administered 30–60 minutes before the first meal of the day. It is not uncommon to find patients taking their PPIs at times convenient to them rather than at the time that enhances the drug’s effects. Thus, explaining to patients the correct dosing time is crucial.

If the patient has dyspepsia at any age with any of the following alarm symptoms:
- chronic GI bleeding
- progressive unintentional weight loss
- progressive dysphagia
- persistent vomiting
- iron-deficiency anaemia
- epigastric mass
- suspicious barium meal

NB: patients aged ≥55 years with unexplained and persistent recent-onset dyspepsia should be referred urgently for endoscopy

**Table 2.** Criteria for urgent endoscopy for suspected cancer, to be completed within two weeks of referral received
Dyspepsia

**Uninvestigated dyspepsia**

**Clinical evaluation:** History and physical examination, determine reason for presentation

*If patient has any of the following:* age >45–55 years, alarm features (unexplained weight loss, bleeding, unexplained anaemia, dysphagia, protracted vomiting), change in character of chronic symptoms, fear of cancer or organic disease

**Consider:** dietary indiscretion, medication-induced dyspepsia, cardiac disease, conditions associated with gastroparesis, hepatobiliary disorders, other systemic disease

**If patient has:** age <45–55 years and no alarm features or chronic, mild symptoms or prior full evaluation

See Figure 3

**Endoscopy with biopsy for H. pylori infection**

**Normal endoscopy result indicating functional dyspepsia**

**Organic disease:** peptic ulcer, GORD, cancer

**Treat as indicated**

**Refractory/disabling symptoms:** psychological therapies, hypnotherapy, referral to psychiatrist or psychologist, consider analgesics

**Symptoms persist**

Consider depression, psychosocial issues

Trial of antidepressant

**Reassurance**

Lifestyle changes

Treat H. pylori infection, if present

Trial of PPI for 2–4 weeks, especially if heartburn or epigastric pain or burning

Trial of prokinetic agent if postprandial fullness and early satiation

Consider IBS (altered bowel habits, abdominal pain)

Figure 2. Assessment and management of uninvestigated dyspepsia
Splitting the dose of PPI to twice daily can be used in cases not responding to once-daily regimens – studies in healthy volunteers have found a divided daily dosage to be either better or not different from once-daily administration. These results may depend on the time of administration of the once-daily dose as well as CYP2C19 genotype. The second dose should be taken prior to the evening meal.

Withdrawal of PPIs can result in rebound acid hypersecretion. In patients treated with PPIs for a period of six months or longer a dose taper should be considered prior to discontinuation. For patients on a moderate to high PPI dose the dose could be reduced by 50 per cent every week. Once on the lowest dose for one week the patient is instructed to stop the medication.

A number of studies have compared the various PPIs and, while there are differences in bioavailability, peak plasma levels and route of excretion, it is unclear whether these differences are of significant clinical importance. One randomised controlled trial (RCT) demonstrated superiority of esomeprazole over omeprazole in healing oesophagitis, although there are no studies demonstrating superiority in dyspepsia. The application of this evidence has to take into the account the higher cost of esomeprazole compared to its counterparts.

New drug developments
There has been considerable interest in developing effective treatments for functional dyspepsia. Recently studied drugs include the 5-HT₄ receptor agonist tegaserod (which was approved by the US Food and Drug Administration in 2002 but subsequently withdrawn in 2007 due to cardiovascular safety concerns), motilin-receptor agonists and ghrelin-receptor agonists. Two agents in particular have been cited in the recent literature: acotiamide and buspirone.

Acotiamide is a new drug developed for the treatment of functional dyspepsia. It enhances acetylcholine release from enteric neurons through muscarinic
Dyspepsia in patients <45–55 years

Alarm features
Family history or ethnic risk of
GI cancer
Excessive worry

yes → Endoscopy

no → Noninvasive \textit{H. pylori} test
Urea breath test
Faecal antigen test
Serology, if above unavailable

\textit{H. pylori} positive:
Eradication therapy

\textit{H. pylori} negative:
Reassurance, lifestyle changes

Symptoms persist:
PPI trial for 2–4 weeks

Improvement:
Stop PPI

If symptoms relapse:
Intermittent or continuous PPI
Consider endoscopy

No improvement:
Endoscopy with biopsy for \textit{H. pylori}

Normal endoscopy result indicating functional dyspepsia:
If \textit{H. pylori} test is still positive, treat with second-line regimen

Organic disease:
GORD, peptic ulcer, cancer

Treat as indicated

Figure 3. Assessment and management of investigated dyspepsia
receptor antagonism and acetylcholinesterase inhibition, thereby enhancing gastric emptying and gastric accommodation. Acotiamide was evaluated in clinical studies in Europe, Japan and the USA. At a dose of 100mg three times a day beneficial effects were observed for the symptoms of postprandial fullness and early satiation. A four-week placebo-controlled phase 3 study in PDS patients in Japan confirmed efficacy of acotiamide in relieving postprandial fullness, early satiation and upper abdominal bloating.10

Buspirone, a 5-HT1A-receptor agonist, relaxes the proximal stomach in healthy individuals. In a randomised double-blind placebo-controlled crossover study of 17 patients with functional dyspepsia, buspirone for four weeks significantly improved symptoms and gastric accommodation compared with placebo.11

As visceral hypersensitivity appears to play a role in functional dyspepsia, antidepressant therapy has been advocated. Several previously published studies as well as a meta-analysis have associated antidepressants with modest benefit against functional dyspepsia.12 So far the strongest evidence of benefit has been with tricyclic antidepressants.13 More recent RCTs utilising venlafaxine (an SNRI) and sertraline (an SSRI) did not show any benefit.14,15 A combination preparation of flupentixol/melitracen has shown promise in a small RCT.16

Conclusion
Dyspepsia is a common symptom with considerable cost burden. Important steps in management include the recognition of alarm signs that necessitate endoscopy, and following the recommended pathways after identifying the cause. Functional dyspepsia can be challenging to manage, but there are some new treatments being developed that may prove efficacious.

References

Declaration of interests
None to declare.

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Resources

Groups and organisations
CORE. Tel: 020 7486 0341; e-mail: info@corecharity.org.uk; website: www.corecharity.org.uk. This national medical charity funds research in the prevention and treatment of digestive disorders and provides information for patients and their families.

British Society of Gastroenterology (BSG). Tel: 020 7935 3150; website: www.bsg.org.uk. The BSG exists to maintain and promote high standards of patient care in gastroenterology.

Guidelines


