

**In this issue:**

<table>
<thead>
<tr>
<th>Dyspepsia symptoms &amp; causes</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appropriate care</td>
<td>1</td>
</tr>
<tr>
<td>Role of community pharmacist</td>
<td>1</td>
</tr>
<tr>
<td>Management strategies (GPs)</td>
<td>2</td>
</tr>
<tr>
<td>Proton Pump Inhibitors</td>
<td>3</td>
</tr>
<tr>
<td>H2 –RAs</td>
<td>4</td>
</tr>
<tr>
<td>Antacids and Alginates</td>
<td>4</td>
</tr>
<tr>
<td>Prokinetic Agents</td>
<td>4</td>
</tr>
<tr>
<td><em>Helicobacter pylori</em></td>
<td>5</td>
</tr>
<tr>
<td>NSAID-induced dyspepsia</td>
<td>6</td>
</tr>
</tbody>
</table>

**Abbreviations**

- GORD: Gastro-Oesophageal Reflux Disease
- H2 –RA: *H2* -Receptor Antagonist
- NNT: Number Needed to Treat
- NSAID: Non-Steroidal Anti-Inflammatory Drug
- OTC: Over-The-Counter
- PPI: Proton Pump Inhibitor
- RCT: Randomised Controlled Trial
- DDD: Defined Daily Dose

## Dyspepsia symptoms & causes

### What is dyspepsia?

Dyspepsia is not a diagnosis, but rather describes a number of symptoms that are thought to originate in the upper gastrointestinal tract.1,2 Dyspepsia is an extremely common disorder in otherwise healthy individuals. Less than half of those with symptoms seek medical care.4-6

There is no single, accepted definition for dyspepsia. In this review a broad definition of dyspepsia is used,2 which one which is relevant and generalisable to primary care.8-10 This definition includes the presence of upper abdominal pain or discomfort, heartburn, acid reflux, nausea and/or vomiting.8,9 The inconsistency in the use of the term dyspepsia by healthcare professionals accounts for the lack of comparability between published studies of dyspepsia. This has been a major barrier to resolving clinical uncertainty about best practice for investigation and treatment of patients.

Any patient presenting with symptoms of dyspepsia who has not been investigated by endoscopy is now classed as having **uninvestigated dyspepsia.**

Where investigation occurs, differentiation is possible leading to diagnoses including:

- Peptic Ulcer Disease (PUD), or
- Non-Ulcer Dyspepsia (NUD), or
- Gastro-Oesophageal Reflux Disease (GORD). GORD can be further subdivided into oesophagitis or Endoscopically Negative Reflux Disease (ENRD).

### What are the common causes of dyspepsia?

Dyspepsia results from disturbance in GI motility, visceral sensation, gastric accommodation, or gastric acid sensitivity and/or psychosocial factors.3 In addition, a small but statistically significant relationship between *Helicobacter pylori* infection and dyspepsia has been observed.11 However, in a large proportion of cases, no clear pathological cause for a patient’s symptoms can be determined.

## Appropriate care

### What is appropriate care for a patient with dyspeptic symptoms?

Given the complex interplay of causes, no single treatment approach provides consistent relief of dyspepsia symptoms. For the vast majority of patients, appropriate care means the management of symptoms with lifestyle advice and medication.

For many patients, self-treatment with antacid and/or alginate therapy (either prescribed or purchased "over the counter") and taken "as required" may continue to be appropriate for immediate symptom relief. However, additional therapy is appropriate to manage symptoms that persistently affect a patient’s quality of life.

Even patients requiring long-term management of dyspepsia symptoms should be encouraged to reduce their use of prescribed medication stepwise; by using the lowest effective dose, by trying as-required use when appropriate, and by returning to self treatment with antacid and/or alginate therapy.1

### What lifestyle modifications can be advised?

Simple lifestyle advice, including advice on healthy diet, weight reduction and smoking cessation should be offered. Patients should be advised to avoid known precipitants associated with their dyspepsia where possible. These may include smoking, alcohol, coffee, chocolate, fatty foods. Raising the head of the bed and having a main meal well before going to bed may help some people.

## The role of the Community Pharmacist

Community pharmacists often provide the first point of contact for dyspepsia sufferers and can offer initial and ongoing help for people suffering from symptoms of dyspepsia. This includes lifestyle changes, using over-the-counter (OTC) medication; help with prescribed drugs and advice about when to consult their GP. (see Chart ONE)

### What medications could community pharmacists recommend for a patient with dyspepsia symptoms?

After confirming the diagnosis and ruling out those patients who may need GP referral (see later), a pharmacist may recommend a suitable treatment based on the nature, severity and frequency of symptoms presented.

Patients experiencing a discrete one-off attack of heartburn symptoms and requiring rapid symptom relief can be recommended a simple antacid preparation, antacid/alginate combination or *H2*–*Receptor antagonist (H2-RAs).12 Patients experiencing recurrent attacks may benefit from omeprazole.12

Omeprazole 10mg tablets (Zanprol®) have been available without prescription since 2004. Community Pharmacists can supply omeprazole 10mg tablets without prescription to people between the ages of 18 and 45 years for the relief of reflux-like symptoms.

### What should patients be advised with regard to onset of symptom relief after starting omeprazole?

Patients should be advised that they may start to experience symptomatic relief after a day or so of starting treatment with omeprazole and that this will increase to a maximum effect after three to four days.

### How should patients be advised to take OTC omeprazole?

Zanprol® are gastro-resistant tablets, which should be swallowed whole with plenty of water before a meal. It is important that the tablets are not crushed or chewed. The starting dose is 20mg (two 10mg tablets) taken once daily for three to four days to obtain symptom relief. When symptoms improve the dose can then be reduced to one 10mg tablet daily, returning to two tablets if symptoms return. The maximum daily dosage is two tablets. If continuous treatment for more than 4 weeks is required to prevent symptoms or no relief is obtained within two weeks then the patient should be referred to their GP.

### Which patients should community pharmacists refer to their GP?

The following patients with dyspepsia symptoms should be referred to their GP:12

- Those aged 45 years or over with new onset of symptoms within the last year which has lasted for at least four weeks or whose symptoms have changed.
- People of any age with "alarm" symptoms (see later).
- Those people who have had to take an antacid or acid suppressor continuously for four weeks or more in order to control their dyspepsia symptoms.
- Patients with any other significant medical condition (including hepatic or renal impairment).
- Pregnant or breast-feeding women.
Chart ONE: Dyspepsia management by community pharmacists

Patient with symptoms of dyspepsia presents at their community pharmacy

Is the patient on any drugs associated with dyspepsia?

- Yes
  - Advise the patient to see their GP routinely

- No
  - Give advice on lifestyle (see text)
    - Response?
      - Adequate
        - Continuing care
      - Inadequate
        - Advice on over-the-counter medicines
          - Response?
            - Inadequate symptomatic relief or prolonged, persistent use
              - Advise the patient to see their GP routinely

Alarm symptoms present?  

- Yes
  - Advise the patient to see their GP as soon as possible

- No
  - Advise the patient to see their GP routinely

Notes

1. Chronic GI bleeding, progressive unintentional weight loss, progressive difficulty swallowing, persistent vomiting.
2. NSAIDs (both to the non-specific and the COX-2 selective NSAIDs), triphosphonates, erythromycin, potassium supplements, acarbose, theophylline and orlistat.

**Dyspepsia Management Strategies in general practice**

**What management strategies could GPs consider for a patient with uninvestigated dyspepsia?**

When a patient presents to their GP with dyspepsia, potential strategies for management include:2,13-15

- endoscopy
- empirical therapy with an acid suppressive drug
- testing for *H. pylori*

Endoscopy yields the greatest diagnostic certainty, directs targeted medical therapy and provides reassurance to both the patient and physician. The cost and small associated risk of complications as well as a lack of infrastructure necessary to endoscope all patients with dyspepsia, however, make endoscopy practical only for selected patients.

Empiric anti-secretory therapy has long been employed as an initial management option in younger patients with uncomplicated uninvestigated dyspepsia. Few studies have directly compared agents. In a study of *H. pylori*-negative patients with uninvestigated dyspepsia from the CADET-HN study, PPIs were found to be more effective than H2-RAs for dyspeptic symptoms (24% vs. 11%, respectively, complete symptom relief at 4 weeks, p < 0.005).16 Likewise, in a double-blind, randomised, multicentre study of patients with acid-related dyspepsia conducted in the UK, superior symptom relief was observed among patients treated with lansoprazole as compared to ranitidine (69% and 44%, respectively, of patients symptom-free at 4 weeks, p=0.001).17

Testing for *H. pylori* helps to decide upon the next management step. This non-invasive approach leads to similar clinical outcomes to prompt endoscopy. If results are negative, patients can be given empirical acid suppression; if the results are positive, patients can undergo either prompt endoscopy or receive empirical *H. pylori* eradication treatment.

While each of the three management options of uninvestigated dyspepsia have advantages and disadvantages, there is broad consensus that routine endoscopy of patients of any age presenting with dyspepsia and without alarm symptoms, is not necessary. However, for any patient presenting with “alarm” features or patients aged 55 years and older with unexplained and persistent recent-onset dyspepsia alone, a referral for endoscopy should be made.1

Why is routine endoscopy not recommended in the absence of “alarm” symptoms?

In two thirds of patients with symptoms of dyspepsia, no gross abnormality is detected on endoscopy.18 It is this large group of patients with a “negative” endoscopy in which the value of the procedure has been questioned. For most people, endoscopic findings will not change the treatment received, and there is a small risk of harm from the procedure.19 In addition, retrospective studies show that upper gastrointestinal malignancy is uncommon in people with dyspepsia (especially below the age of 55 years) and when it is found, it is often associated with a poor prognosis. It is not clear whether early detection of upper gastrointestinal cancers improves outcomes.20-24

On initial presentation with dyspepsia symptoms, which patients need an initial referral for endoscopy?

Immediate (same day) referral is indicated for patients presenting with dyspepsia together with significant acute GI bleeding.

Urgent specialist referral or endoscopic investigation (within 2 weeks) is indicated for patients of any age with dyspepsia when presenting with any of the “alarm” signs. Additionally, in patients aged 55 years and older with unexplained and persistent recent-onset dyspepsia alone, a referral for endoscopy should be made.1

What are “alarm” signs or symptoms?

- Chronic GI bleeding.
- Progressive unintentional weight loss.
- Progressive difficulty swallowing.
- Persistent vomiting.
- Iron deficiency anaemia.
- Epigastric mass.
- Suspicious barium meal.

Alarm symptoms are present in 10% of people presenting with dyspepsia in primary care25 and have traditionally been used as predictors for major pathology in patients with dyspepsia (e.g., ulcer with complications or upper GI cancer).
**Should treatment be offered to a patient awaiting routine endoscopy?**

If the person is not currently taking treatment but has to wait for investigation, it is reasonable to offer a single course of treatment. Antacids or alginates are preferred or alternatively a 2-4 week course of an H2-RA could be used. PPIs are probably best avoided in this situation.\(^2\) Importantly, PPIs and H2-RAs should be stopped at least 2 weeks before endoscopy, because acid suppression therapy can mask or delay the detection of gastric and oesophageal adenocarcinoma.\(^1\) Antacids and alginates do not need to be stopped before the endoscopy.

**Should “test and treat” or empiric anti-secretory therapy be first-line?**

Several factors influence the choice between the test-and-treat strategy and empiric anti-secretory therapy. These include:

- the local prevalence of *H. pylori* and peptic ulcer disease,
- the proportion of ulcers attributable to *H. pylori*,
- the cost and success of diagnostic testing and therapy.

NICE would consider that there is currently insufficient evidence to guide which strategy should be offered first.

The economic implication of the two competing strategies for uninvestigated dyspepsia was evaluated in a cost-minimisation analysis model in which PPI treatment was consistently less costly than test-and-treat when the *H. pylori* prevalence was less than 20%.\(^27\)

World-wide consensus conferences have adopted a strategy of screening uninvestigated dyspepsia patients without alarm symptoms under the age of 45-55 years with a non-invasive *H. pylori* test, and treating patients with positive results with *H. pylori* eradication therapy.\(^9,15\)

**Which medication might be causing dyspepsia?**

Many medications can potentially induce dyspepsia. However, there is no strong evidence that any group of drugs aside from NSAIDs (both non-specific and the COX-2 selective NSAIDs),\(^28,30\) are major causes of dyspepsia in the community.\(^71\) Bisphosphonates can also induce ulceration and dyspepsia. Other agents including erythromycin, potassium supplements (particularly modified-release forms), acarbose, theophylline and orlistat may sometimes cause dyspepsia.

---

**Pharmacological management of uninvestigated dyspepsia**

**Are PPIs effective when used empirically in dyspepsia?**

Meta-analysis of RCTs in non-ulcer dyspepsia found a significant benefit of PPIs versus placebo, with an NNT=7, meaning that 7 patients must be treated to achieve benefit in 1 additional patient compared with placebo.\(^32\)

PPIs are more effective than antacids at reducing dyspeptic symptoms in trials of patients with uninvestigated dyspepsia.\(^33,34\) Pooled results indicate that the average rate of response taking an antacid was 37% and PPI therapy increased this to 55%; for every 6 people treated there was one additional responder (NNT=6).\(^3,38\)

PPIs are more effective than H2-RAs at reducing dyspeptic symptoms.\(^15,24,36\) Pooled results show an average response rate in H2-RA groups was 36% and PPI increased this to 58%; for every 5 people treated there was one additional responder (NNT=5).\(^1,36\)

For heartburn symptoms, Cochrane showed the NNTs were 3.5 (95%CI 3.0 to 4.2) for PPI over antacids and 3.1 (95%CI 2.7 to 3.9) for PPI versus H2-RA.\(^35\)

**Which PPI?**

Differences between the PPIs in clinical efficacy and safety are minimal.\(^37,39\) On present evidence, PPIs do not have any serious contraindications for most users, and have been in common use for over a decade. PPIs are an effective treatment for uninvestigated dyspepsia symptoms.\(^1\) The newer PPIs offer no advantage in terms of clinical efficacy over more established PPIs, are generally more expensive, and have less evidence of long term safety. Omeprazole and Lansoprazole are well-established agents and have the advantage of being available generically. PPIs are generally well tolerated. Adverse effects include gastrointestinal disturbances (most commonly diarrhoea), headaches, and dizziness. PPIs undergo extensive hepatic metabolism. In liver disease, do not exceed the following doses: 20 mg daily for omeprazole, pantoprazole, and esomeprazole, 30 mg daily for lansoprazole. There are no data on the use of rabeprazole in people with severe hepatic impairment so the manufacturer advises caution.

**What have the results of the CADET-HN study contributed to the decision on which PPI?**

According to the results of the CADET-HN study,\(^15\) treatment of dyspepsia symptoms (in *H. pylori* negative primary care patients) with omeprazole provides superior symptom relief to that achieved with ranitidine or with cisapride. The 512 patients with moderate to severe symptoms were randomised to receive omeprazole 20mg daily, or ranitidine 150mg twice daily, or cisapride 20mg twice daily, or placebo for 4 weeks, followed by on-demand therapy for an additional 5 months. Treatment success was defined as no or minimal symptoms. The researchers reported the following success rates at 4 weeks (95%CI):

- omeprazole 51% (43-60%),
- ranitidine 36% (28-44%),
- cisapride 31% (22-39%), and
- placebo 23% (16-31%).

Omeprazole was better than all other treatments (p < 0.05).\(^1\)

**Which dose?**

Table ONE gives PRODIGY-recommended PPI doses for uninvestigated dyspepsia symptoms.

**How effective are PPIs when given on an “on-demand” basis?**

The evidence for using ‘on-demand’ PPI therapy in people with uninvestigated dyspepsia is extrapolated from studies looking at people with ENRD. The patient populations are similar and, in the absence of “alarm” symptoms, this extrapolation is a safe step.\(^7,9\) Such studies show that intermittent use is clinically effective and is considered to be safe.\(^6,14\)

‘On-demand’ PPI therapy is effective, and less costly than continuous therapy.\(^1\) But therapy can (and should) be individualised, as a proportion of people will continue to take their PPI daily.

---

**Prescribing of Proton Pump Inhibitors in Primary Care in Northern Ireland (Data from Pharmaceutical Dept. CSA, Belfast)**

<table>
<thead>
<tr>
<th>Year</th>
<th>Esomeprazole</th>
<th>Lansoprazole</th>
<th>Omeprazole</th>
<th>Pantoprazole</th>
<th>Rabeprazole Sodium</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>4.0</td>
<td>8.0</td>
<td>8.0</td>
<td>4.0</td>
<td>1.0</td>
</tr>
<tr>
<td>2001</td>
<td>4.2</td>
<td>8.1</td>
<td>7.0</td>
<td>4.1</td>
<td>1.1</td>
</tr>
<tr>
<td>2002</td>
<td>4.3</td>
<td>8.2</td>
<td>7.1</td>
<td>4.2</td>
<td>1.2</td>
</tr>
<tr>
<td>2003</td>
<td>4.4</td>
<td>8.3</td>
<td>7.2</td>
<td>4.3</td>
<td>1.3</td>
</tr>
<tr>
<td>2004</td>
<td>4.5</td>
<td>8.4</td>
<td>7.3</td>
<td>4.4</td>
<td>1.4</td>
</tr>
<tr>
<td>2005</td>
<td>4.6</td>
<td>8.5</td>
<td>7.4</td>
<td>4.5</td>
<td>1.5</td>
</tr>
</tbody>
</table>

PPIs have adopted a strategy of screening uninvestigated dyspepsia patients and orlistat may sometimes cause dyspepsia.

---

**Proton pump inhibitors (PPIs)**

- Esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole

---

**Endoscopy**

- **Economic implication of the two competing strategies for uninvestigated dyspepsia**
- **Which medication might be causing dyspepsia?**
- **Which PPI?**
- **What have the results of the CADET-HN study contributed to the decision on which PPI?**
- **Which dose?**
- **How effective are PPIs when given on an “on-demand” basis?**

---

**Further copies at www.centralservicesagency.n-i.nhs.uk/display/compass**
How should patients be advised to take "on-demand" therapy?

"On-demand" therapy is where treatment is taken, when required, in response to symptoms. Once symptoms are relieved (often after a few days) treatment is stopped again. In contrast, some people may prefer intermittent therapy. This refers to a 2-4 week course of treatment for recurring symptoms.1,2

Although none of the PPIs in use in the UK are currently licensed for on-demand treatment in uninvestigated dyspepsia, esomeprazole, pantoprazole and rabeprazole are licensed for on-demand treatment in GORD. In addition, on-demand use is recommended by NICE.1

What drug interactions have been reported with PPIs?

Antacids may cause a slight reduction in the bioavailability of lansoprazole. This is probably not clinically relevant but can be accommodated by separating their administration.43

Clarithromycin almost doubles the serum levels of omeprazole and esomeprazole. No adverse effects of the interaction have been reported.43,44

Omeprazole levels are markedly increased by ketoconazole45 and fluconazole46 and voriconazole.47 When initiating voriconazole in patients already receiving omeprazole, it is recommended that the omeprazole dose be halved.47 Dose reductions are not required when omeprazole is co-administered with ketoconazole or fluconazole.46

Occasionally and unpredictably, bleeding occurs in patients on warfarin who are co-prescribed esomeprazole, lansoprazole or omeprazole.43 Thus it is probably prudent to monitor the INR of any patient on warfarin when starting or stopping treatment with a PPI.

PPI Prescribing Points

Differences between the PPIs in clinical efficacy and safety are minimal.

• Omeprazole and lansoprazole are available generically.
• Omeprazole, lansoprazole and esomeprazole are licensed for on-demand use in the UK are currently licensed for on-demand use in the UK.

H2-Receptor Antagonists (H2-RAs)

Cimetidine, famotidine, nizatidine and ranitidine

Are there any important adverse effects or interactions with H2-RAs?

Adverse effects are uncommon but have included diarrhoea, headache, dizziness, rash, and tiredness. Cimetidine should be avoided in people taking erythromycin, warfarin, amiodarone, theophylline, carbamazepine, phenytoin, and

sodium valproate as cimetidine inhibits hepatic drug metabolism by binding to microsomal cytochrome P450.

Are H2-RAs effective in the management of uninvestigated dyspepsia?

The H2-RAs have been shown to be more effective than placebo in the management of people with uninvestigated dyspepsia. A Cochrane meta-analysis of 11 RCTs studying the effects of H2-RAs in non-ulcer dyspepsia showed a significant benefit of H2-RAs over placebo, with a relative risk reduction of 22% (95% CI 7-35%). The estimated NNT was 8. However, these data need to be interpreted with caution given the majority of the trials included were small and heterogeneous in nature.52

Which H2-RA is preferred?

Ranitidine is the agent of choice among the H2-RAs. Unlike cimetidine, ranitidine does not affect cytochrome P450 to any great extent, therefore, it is considered to have little effect on the metabolism of other drugs.48

Antacids and alginate

There is limited evidence on the efficacy of antacids in the management of dyspepsia; however, symptomatic relief is often reported with the use of an antacid or alginate.

Antacids and alginate are best given when symptoms occur or are expected, i.e. after meals and at bedtime. They also remain in the stomach for longer at these times and, therefore, have longer to act.

PPI Prescribing Points

Differences between the PPIs in clinical efficacy and safety are minimal.

• Omeprazole and lansoprazole are available generically.
• Omeprazole, lansoprazole and esomeprazole are licensed for on-demand use in the UK are currently licensed for on-demand use in the UK.

H2-Receptor Antagonists (H2-RAs)

Cimetidine, famotidine, nizatidine and ranitidine

Are there any important adverse effects or interactions with H2-RAs?

Adverse effects are uncommon but have included diarrhoea, headache, dizziness, rash, and tiredness. Cimetidine should be avoided in people taking erythromycin, warfarin, amiodarone, theophylline, carbamazepine, phenytoin, and

sodium valproate as cimetidine inhibits hepatic drug metabolism by binding to microsomal cytochrome P450.

Are H2-RAs effective in the management of uninvestigated dyspepsia?

The H2-RAs have been shown to be more effective than placebo in the management of people with uninvestigated dyspepsia. A Cochrane meta-analysis of 11 RCTs studying the effects of H2-RAs in non-ulcer dyspepsia showed a significant benefit of H2-RAs over placebo, with a relative risk reduction of 22% (95% CI 7-35%). The estimated NNT was 8. However, these data need to be interpreted with caution given the majority of the trials included were small and heterogeneous in nature.52

Which H2-RA is preferred?

Ranitidine is the agent of choice among the H2-RAs. Unlike cimetidine, ranitidine does not affect cytochrome P450 to any great extent, therefore, it is considered to have little effect on the metabolism of other drugs.48

Antacids and alginate

There is limited evidence on the efficacy of antacids in the management of dyspepsia; however, symptomatic relief is often reported with the use of an antacid or alginate.

Antacids and alginate are best given when symptoms occur or are expected, i.e. after meals and at bedtime. They also remain in the stomach for longer at these times and, therefore, have longer to act.

Prescribing Point

Antacids should preferably not be taken at the same time as other drugs as they may impair absorption.

Most antacids contain aluminium salts, magnesium salts, or a combination of the two. Combinations of aluminium salts with magnesium salts may be preferable to magnesium salts alone (which may cause diarrhoea) or aluminium salts alone (which may cause constipation).

Alginates form a ‘raft’ that floats on the surface of the stomach contents. They are most useful for people with mild reflux symptoms.

Prokinetic agents

Domperidone and metoclopramide

Domperidone and metoclopramide are both used as prokinetic agents to reduce symptoms such as bloating and early satiety.

Why should the long-term use of prokinetic agents be avoided?

There is an increased risk of hyperprolactinaemia (e.g. galactorrhoea, gynaecomastia, and amenorrhoea) with both domperidone and metoclopramide. Chronic use of metoclopramide increases the risk of extrapyramidal adverse effects (i.e. drug-induced acute dystonic reactions).

Domperidone is a dopamine antagonist with peripheral actions only, and thus it is devoid of the central side-effects associated with metoclopramide.49

What way should patients take prokinetic agents?

Encourage people using prokinetics to use them as on-demand or intermittent therapy.

Are there any patient groups in whom prokinetic agents should be avoided?

Metoclopramide should be avoided in young adults (under the age of 20 years) because of the increased risk of extrapyramidal adverse effects in this age group.

Metoclopramide crosses the blood-brain barrier and often causes CNS side effects, including drowsiness (up to 20% of patients), anxiety, depression and extrapyramidal symptoms. In the elderly, an increased risk of irreversible tardive dyskinesia has been reported.50-52

Is there evidence for the use of metoclopramide in dyspepsia?

There are only limited data suggesting efficacy of metoclopramide in non-ulcer dyspepsia.53-56 Reports suggest arrhythmogenic properties of this compound,57 and on these grounds, the use of metoclopramide in uninvestigated dyspepsia should not be first choice.
The role of Helicobacter pylori in uninvestigated dyspepsia

What is Helicobacter pylori and what is its role in dyspepsia?
Helicobacter is a Gram negative, flagellated, spiral bacterium found in the stomach. Infection with H. pylori is predominantly acquired in childhood. Although a causal link between H. pylori and peptic disease, gastritis, duodenitis and gastric cancer is well recognised, the role of the infection in dyspepsia and the effectiveness of eradication therapy on dyspeptic symptoms are more controversial.

Testing for Helicobacter pylori in primary care

Testing for H. pylori in patients in primary care?
Guidelines for managing dyspepsia recommend the use of non-invasive tests for H. pylori detection at the out set.

How can we test for H. pylori in primary care?
Exclusion of H. pylori is important for the management of dyspepsia. The presence of H. pylori might lead to a false disease at a diagnosis or a false positive test. Up to 25% of people with dyspepsia are H. pylori positive. Laboratory serological tests are more accurate than laboratory based serological tests.

Why is laboratory-based serological testing for H. pylori probably not the best choice of test in primary care?
Laboratory-based serological tests measure H. pylori antibody levels that can persist for up to two years after successful eradication. This can lead to false positive tests. Up to 25% of serological H. pylori test results have been found to be false positives. The availability of accurate breath tests has led some authors to suggest that the use of laboratory-based serological tests is no longer justified.

Do these tests vary with regard to their sensitivity and specificity?
Studies have consistently shown that 13C-urea breath tests and stool antigen tests are more accurate than laboratory based serological tests. (See Table TWO).

Which H. pylori test should be first choice in primary care?
NICE recommends the use of a 13C-urea breath test or a stool antigen test for pre-treatment testing. However, 13C-urea breath tests are available on prescription and are likely to be more acceptable to patients than stool antigen testing. Stool antigen tests and 13C-urea breath tests cost more to perform than laboratory-based serological tests but any additional cost to the healthcare provider will be offset by improved diagnostic accuracy.

Eradicating H. pylori in primary care

Following H. pylori eradication therapy, is re-testing recommended?
H. pylori re-testing after eradication therapy is not routinely recommended in people with uninvestigated dyspepsia unless there is a strong clinical need (e.g. family history of gastric cancer).

What is the evidence for H. pylori "test and treat" in uninvestigated dyspepsia?
There is growing support for the use of "test and treat" strategy as a simple, non-invasive and cost effective option based on the fact that a wide eradication of the bacterium at least might lead to prevention of peptic disease.

Table TWO: Accuracy of non-invasive tests for H. pylori infection

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity* for Active Infection (%)</th>
<th>Specificity* for Active Infection (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13C-urea breath test</td>
<td>94.7</td>
<td>95.7</td>
</tr>
<tr>
<td>Stool antigen testing</td>
<td>93.1</td>
<td>92.8</td>
</tr>
<tr>
<td>Laboratory serological tests</td>
<td>85</td>
<td>79</td>
</tr>
</tbody>
</table>

* Sensitivity is the proportion of true positives that are correctly identified by the test, whereas specificity is the proportion of true negatives that are correctly identified by the test.

Prescribing Points
Neither breath tests nor stool antigen tests should be performed within 2 weeks of antibiotic therapy or within 4 weeks of antibiotic therapy, as false-negative results may occur.

If the person is taking long-term antibiotics: phenoxymethylpenicillin, nitrofurantoin, and trimethoprim are not active against H. pylori, so will not affect the test results. Tetracyclines, macrolides, broad-spectrum penicillins (e.g. amoxicillin), cephalosporins, and anti-tuberculosis drugs are all active against H. pylori. Advice should be sought from the local microbiology laboratory on interpretation if people are taking long-term antibiotics other than phenoxymethylpenicillin, nitrofurantoin or trimethoprim.

Does H. pylori eradication improve the symptoms of dyspepsia?
A Cochrane Systematic review attempted to answer this question. This review suggested that H. pylori eradication therapy reduces symptoms in patients with non-ulcer dyspepsia. The impact on symptoms was statistically significant but the effect size was small.

Which H. pylori eradication regimen should be used?
For patients who test positive for H. pylori, a seven-day, course of triple therapy is recommended. This consists of:
- A full dose PPI, plus
- Clarithromycin, plus either
- Metronidazole (known as a PCM regimen) or amoxicillin (known as a PAC regimen).

Table THREE indicates the doses used in PCM and PAC regimens. Data for these regimens show no statistically significant difference in eradication rates and are effective in 80-85% of patients.
Which eradication regimen should be used if the patient has had a recent course of antibiotics?

An alternative antibiotic should be used in the eradication regimen if a course of clarithromycin or metronidazole has previously been given (for any indication) within the previous four weeks.

The HPA Helicobacter Working Group recommends that two antibiotics are chosen from the following options: amoxicillin, clarithromycin, metronidazole, or omeprazole. Other antibiotics can be considered, but advice should be sought from the Helicobacter Reference Laboratory (telephone 0208 327 6538).

Is resistance to antibiotics emerging in H. pylori?

Resistance of H. pylori to antibiotics (especially metronidazole and clarithromycin) is a problem, and its prevalence seems to be increasing. Laboratory testing suggests that H. pylori antibiotic resistance is around 15-66% for metronidazole, and 8-30% for clarithromycin. Data on H. pylori resistance to amoxicillin have not been published.

Whether this increase is caused by antibiotic use in H. pylori eradication or by the prescription of antibiotics for other indications is not known. Because the current H. pylori eradication regimens are so effective, induction of resistance should be a rare event, provided that the regimen is properly prescribed and time is taken to instruct and motivate the patient.

Prescribing Points – H. pylori eradication

Remind people that it is important to complete the course.

Advise people taking metronidazole to avoid alcohol for the duration of the course and for at least 48 hours afterwards, because of the possibility of a disulfiram-like (Antabuse) reaction.

Clarithromycin inhibits the metabolism of other drugs and can prolong the QT interval. Check drug interactions before prescribing.

Who needs to be referred for endoscopy if symptoms persist?

In people of any age with difficult to control or persistent dyspeptic symptoms (i.e. both control symptoms and motivate the patient.78

Managing dyspepsia associated with Non Steroidal Anti-Inflammatory Drugs (NSAIDs)

How can NSAID-induced dyspepsia be managed?

Wherever possible the NSAID should be stopped. If this is not possible, consider using strategies to reduce NSAID use:

- Offer a trial of NSAID-use on a limited ‘as required’ basis.
- Dose reduction.

Should a patient experiencing NSAID-induced dyspepsia be referred for endoscopy?

In the absence of ‘alarm’ features referral for endoscopy is unnecessary. However a referral may be considered if:

- There is a strong suspicion of ulcer.
- Symptoms persist despite H. pylori testing and acid suppression in a person over 55 years of age.
- The person is aged over 65 years and has 1 additional risk factor for NSAID complications. (See Box ONE)
- The person is aged less than 65 years and has 2 additional risk factors for NSAID complications. (See Box ONE)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Pooled RR</th>
<th>95% CI for pooled RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>1.9</td>
<td>1.6-2.2</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>3.3</td>
<td>2.8-3.9</td>
</tr>
<tr>
<td>Sulindac</td>
<td>3.6</td>
<td>2.8-4.7</td>
</tr>
<tr>
<td>Naproxen</td>
<td>4.0</td>
<td>3.5-4.6</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>4.6</td>
<td>3.8-5.5</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>4.6</td>
<td>3.3-6.4</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>6.3</td>
<td>5.5-7.2</td>
</tr>
</tbody>
</table>

Table FOUR: Pooled relative risks (RR) for upper GI bleed for users of NSAIDs compared with non-users for studies 1990-1999.88

Box ONE: Risk factors for NSAID-induced dyspepsia

- Age over 65 years.
- Previous history of peptic ulcer disease, gastrointestinal bleeding or perforation.
- Patient also taking corticosteroids, anticoagulants, or low-dose aspirin.
- Taking maximum doses of NSAIDs for a long duration.
- Serious co-morbidity such as cardiovascular disease or diabetes.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Pooled RR</th>
<th>95% CI for pooled RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>1.9</td>
<td>1.6-2.2</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>3.3</td>
<td>2.8-3.9</td>
</tr>
<tr>
<td>Sulindac</td>
<td>3.6</td>
<td>2.8-4.7</td>
</tr>
<tr>
<td>Naproxen</td>
<td>4.0</td>
<td>3.5-4.6</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>4.6</td>
<td>3.8-5.5</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>4.6</td>
<td>3.3-6.4</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>6.3</td>
<td>5.5-7.2</td>
</tr>
</tbody>
</table>

Table THREE: Regimens for H. pylori eradication

<table>
<thead>
<tr>
<th>PPI</th>
<th>Amoxicillin 1gram twice daily</th>
<th>Clarithromycin*</th>
<th>Metronidazole 400mg twice daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esomeprazole 20mg twice daily</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Lansoprazole 30mg twice daily</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Omeprazole 20mg twice daily</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Pantoprazole 40mg twice daily</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Rabeprazole 20mg twice daily</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
</tbody>
</table>

Note: The dose of clarithromycin differs between the PAC and PCM regimens. Pooled data for PAC regimens show eradication rates of 79.8% with clarithromycin 250 mg versus 89.6% with clarithromycin 500 mg. In PCM regimens, doubling the dose of clarithromycin had no statistically significant effect: eradication rates were 87.4% for clarithromycin 250mg and 88.9% for clarithromycin 500mg.

Table FOUR: Pooled relative risks (RR) for upper GI bleed for users of NSAIDs compared with non-users for studies 1990-1999.88

Agent | Pooled RR | 95% CI for pooled RR |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>1.9</td>
<td>1.6-2.2</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>3.3</td>
<td>2.8-3.9</td>
</tr>
<tr>
<td>Sulindac</td>
<td>3.6</td>
<td>2.8-4.7</td>
</tr>
<tr>
<td>Naproxen</td>
<td>4.0</td>
<td>3.5-4.6</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>4.6</td>
<td>3.8-5.5</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>4.6</td>
<td>3.3-6.4</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>6.3</td>
<td>5.5-7.2</td>
</tr>
</tbody>
</table>

Should a patient experiencing NSAID-induced dyspepsia be referred for endoscopy?

In the absence of ‘alarm’ features referral for endoscopy is unnecessary. However a referral may be considered if:

- There is a strong suspicion of ulcer.
- Symptoms persist despite H. pylori testing and acid suppression in a person over 55 years of age.
- The person is aged over 65 years and has 1 additional risk factor for NSAID complications. (See Box ONE)
- The person is aged less than 65 years and has 2 additional risk factors for NSAID complications. (See Box ONE)

Box ONE: Risk factors for NSAID-induced dyspepsia

- Age over 65 years.
- Previous history of peptic ulcer disease, gastrointestinal bleeding or perforation.
- Patient also taking corticosteroids, anticoagulants, or low-dose aspirin.
- Taking maximum doses of NSAIDs for a long duration.
- Serious co-morbidity such as cardiovascular disease or diabetes.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Pooled RR</th>
<th>95% CI for pooled RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>1.9</td>
<td>1.6-2.2</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>3.3</td>
<td>2.8-3.9</td>
</tr>
<tr>
<td>Sulindac</td>
<td>3.6</td>
<td>2.8-4.7</td>
</tr>
<tr>
<td>Naproxen</td>
<td>4.0</td>
<td>3.5-4.6</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>4.6</td>
<td>3.8-5.5</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>4.6</td>
<td>3.3-6.4</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>6.3</td>
<td>5.5-7.2</td>
</tr>
</tbody>
</table>

Table FOUR: Pooled relative risks (RR) for upper GI bleed for users of NSAIDs compared with non-users for studies 1990-1999.88

Agent | Pooled RR | 95% CI for pooled RR |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>1.9</td>
<td>1.6-2.2</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>3.3</td>
<td>2.8-3.9</td>
</tr>
<tr>
<td>Sulindac</td>
<td>3.6</td>
<td>2.8-4.7</td>
</tr>
<tr>
<td>Naproxen</td>
<td>4.0</td>
<td>3.5-4.6</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>4.6</td>
<td>3.8-5.5</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>4.6</td>
<td>3.3-6.4</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>6.3</td>
<td>5.5-7.2</td>
</tr>
</tbody>
</table>

Should a patient experiencing NSAID-induced dyspepsia be referred for endoscopy?

In the absence of ‘alarm’ features referral for endoscopy is unnecessary. However a referral may be considered if:

- There is a strong suspicion of ulcer.
- Symptoms persist despite H. pylori testing and acid suppression in a person over 55 years of age.
- The person is aged over 65 years and has 1 additional risk factor for NSAID complications. (See Box ONE)
- The person is aged less than 65 years and has 2 additional risk factors for NSAID complications. (See Box ONE)

Box ONE: Risk factors for NSAID-induced dyspepsia

- Age over 65 years.
- Previous history of peptic ulcer disease, gastrointestinal bleeding or perforation.
- Patient also taking corticosteroids, anticoagulants, or low-dose aspirin.
- Taking maximum doses of NSAIDs for a long duration.
- Serious co-morbidity such as cardiovascular disease or diabetes.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Pooled RR</th>
<th>95% CI for pooled RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>1.9</td>
<td>1.6-2.2</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>3.3</td>
<td>2.8-3.9</td>
</tr>
<tr>
<td>Sulindac</td>
<td>3.6</td>
<td>2.8-4.7</td>
</tr>
<tr>
<td>Naproxen</td>
<td>4.0</td>
<td>3.5-4.6</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>4.6</td>
<td>3.8-5.5</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>4.6</td>
<td>3.3-6.4</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>6.3</td>
<td>5.5-7.2</td>
</tr>
</tbody>
</table>

Should a patient experiencing NSAID-induced dyspepsia be referred for endoscopy?

In the absence of ‘alarm’ features referral for endoscopy is unnecessary. However a referral may be considered if:

- There is a strong suspicion of ulcer.
- Symptoms persist despite H. pylori testing and acid suppression in a person over 55 years of age.
- The person is aged over 65 years and has 1 additional risk factor for NSAID complications. (See Box ONE)
- The person is aged less than 65 years and has 2 additional risk factors for NSAID complications. (See Box ONE)

Box ONE: Risk factors for NSAID-induced dyspepsia

- Age over 65 years.
- Previous history of peptic ulcer disease, gastrointestinal bleeding or perforation.
- Patient also taking corticosteroids, anticoagulants, or low-dose aspirin.
- Taking maximum doses of NSAIDs for a long duration.
- Serious co-morbidity such as cardiovascular disease or diabetes.
How should patients with dyspepsia who need to remain on an NSAID be managed?
If continued NSAID use is still necessary:
- Remind people that NSAIDs should be taken with or after food.
- Test for H. pylori and (if the result is positive) eradicate (as above).
- Use gastroprotection (see later)
- Offer symptomatic treatment with a PPI to people without risk factors for NSAID complications.

Why should a patient experiencing NSAID-induced dyspepsia be tested for H. pylori?
There are many conflicting data about the influence of H. pylori infection on the ulcer risk in patients receiving NSAIDs. To date there are studies showing that the interaction between H. pylori and NSAIDs in ulcer development is synergistic, additive, independent or antagonistic! These conflicting results can not be accounted for by the heterogeneity of study designs and the diversified host response to H. pylori.

In people taking NSAIDs with persistent or recurrent dyspepsia consider testing for H. pylori.
In people without previous ulcers, H. pylori is 150 mg reduced the risk of NSAID-induced peptic ulcers compared to placebo, and was as effective as acid suppression in reducing this risk.

What is the preferred gastroprotection for use along with an NSAID?
A PPI (preferably one which is available generically such as omeprazole or lansoprazole) must be at full dose is generally considered to be an effective use of NHS resources. Above £30,000/QALY the case for the supporting technology has to be increasingly strong.

Summary of NICE guidance for the management of dyspepsia
The essential messages in the NICE guideline for the management of dyspepsia in adults are as follows:
- Patients who present to their GP with symptoms of dyspepsia that have not previously been investigated should be managed empirically (test and treat for H. pylori or one month’s treatment with a PPI at the full recommended dose). Such patients do not routinely require referral for endoscopy.
- Thereafter, patients should be encouraged to use the prescribed treatment on an “on demand” basis in order to manage their own symptoms. In other words, take therapy only when their symptoms occur.
- Long-term management of dyspepsia should include the offer of an annual review by their GP, during which patients should be encouraged to “step-down” or even stop treatment altogether.
- Self-treatment with an antacid and/or alginate, taken as required, may be appropriate for many patients. Additional therapy may be appropriate to manage symptoms that persistently affect a patient’s quality of life.
- Urgent specialist referral or endoscopic investigation (to be seen within two weeks) is only indicated for those presenting with alarm symptoms.
- If patients over the age of 55 years do not respond to initial empirical therapy, or if the risk of gastric cancer is heightened, referral for endoscopy may be considered.

The full guidance can be found at www.nice.org.uk.

Reference List

Have there been any studies looking at the cost-effectiveness of strategies to prevent NSAID-induced gastric toxicity?
A recent systematic review on gastroprotection with a cost utility analysis showed that:
- The incremental increase in QALYs gained by using a COX-2 selective NSAID instead of a non-selective NSAID along with a H2-RA would cost £670,000 per QALY gained.
- The incremental increase in QALYs gained by giving a PPI along with a non-selective NSAID instead of a COX-2 selective NSAID would cost £26,000 per QALY gained.

[Incremental cost per QALY of £20,000 or less is generally considered to be an effective use of NHS resources. Above £30,000/QALY the case for the supporting technology has to be increasingly strong.]

Prescribing Point – Misoprostol
Misoprostol should not be used in women of childbearing age unless the patient requires an NSAID and is at high risk of complications from NSAID-induced ulceration. In such patients it is advised that misoprostol should only be used if the patient takes effective contraceptive measures and has been advised of the risks of taking misoprostol if pregnant.