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**D** DYSPEPSIA & HEARTBURN  
**POEMs**



# Dyspepsia & Heartburn POEMs

Patient Oriented Evidence that Matters

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All information is intended for use by competent health care professionals and should be utilized in conjunction with pertinent clinical data.

## Summary

1. **Functional dyspepsia:** Not all patients with functional dyspepsia require drug treatment. No drug therapies have been found to have a high success rate. There is a substantial placebo response. Drug treatment such as antacids, H<sub>2</sub> receptor antagonists or prokinetic agents, should usually be given on a short term basis only.
2. **GORD:** Heartburn has a 75% association with gastro-oesophageal reflux disease (GORD). Over half of patients with GORD will have no evidence of mucosal breaks at oesophagoscopy. After the initial acute treatment phase, aim to maintain on the least amount of medication e.g. low dose or intermittent therapy with either a proton pump inhibitor or H<sub>2</sub> receptor antagonist. Not all patients will require maintenance therapy.
3. **Peptic ulcer disease:** Eradication of *Helicobacter pylori* is the mainstay of management. Continued maintenance therapy after successful eradication should only be required in a minority of patients. Aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) account for most of the ulcers not associated with *H. pylori*.
4. **Traditional NSAIDs** are associated with gastro-intestinal toxicity. Proton pump inhibitors can be co-prescribed to provide gastric protection. COX-2 inhibitors are only cost effective in selected at risk cases, they have adverse effects in common with traditional NSAIDs, and should not be used in patients taking aspirin for cardioprotection. There is no evidence to justify the simultaneous use of gastro-protective drugs with COX-2 inhibitors.
5. **Proton pump inhibitors** are associated with considerable cost. It is probably not the healing or acute phase treatment, but the repeat prescriptions for maintenance treatment that drives the increasing cost. Long term maintenance proton pump inhibitor treatment should be reviewed.

*When is long term proton pump inhibitor treatment appropriate?*

- *Maintenance treatment of the more severe grades of GORD or with frequent recurrences e.g. within 3 months. The lowest effective dose should be used.*
- *For gastric protection when NSAID use cannot be discontinued in high risk individuals.*
- *Complicated disease (stricture, ulcer, haemorrhage) or Barrett's oesophagitis.*

*When is long term proton pump inhibitor treatment **not** appropriate?*

- *Functional dyspepsia (no drug treatment is recommended long term).*
- *After successful eradication of *H. pylori* associated with peptic ulcer.*
- *In patients without investigation or a confirmed diagnosis.*

6. **Alarm features** include: dysphagia, evidence of gastrointestinal blood loss, persistent severe pain or vomiting, unexplained weight loss and upper abdominal mass, NSAID use in at risk patients, and a family history of gastric cancer below age 50 years.

## Approach to Symptoms

### Dyspepsia & Heartburn Symptoms

- Investigate**
- All people presenting with alarm signals (see below).
  - Consider referral and investigation if aged >50 years at first presentation.
  - When response to treatment is poor.
  - If maintenance PPI treatment is being considered without a confirmed diagnosis.

**Treat** Empiric treatment prior to considering investigation is justified for many patients.

Functional dyspepsia:

- Provide reassurance & lifestyle advice.
- Initial short trial (≈4 weeks) of an antacid, H<sub>2</sub>RA or prokinetic agent.
- Consider “test and treat” with a view to eradicate *H. pylori* in areas of high prevalence (>30%).

GORD:

- Initial acute treatment (8-12 weeks) with acid suppressant e.g. PPI or H<sub>2</sub>RA.
- Maintenance treatment stepped down to the requirements of the patient (e.g. continuous low dose, intermittent or on-demand therapy or even no maintenance therapy).

Peptic ulcer:

- *H. pylori* positive: eradication therapy.
- *H. pylori* negative: 8 weeks for duodenal ulcer or 12 weeks for gastric ulcer of PPI or H<sub>2</sub>RA treatment.
- Long term acid suppressing therapy should not be required in the majority of patients.

- Review**
- If a patient fails to respond to treatment refer for investigation.
  - Step down therapy in patients who remain asymptomatic on maintenance treatment (aim for the lowest effective dose of the least potent agent or no therapy).
  - Consider a treatment-free trial with intermittent or on-demand use of medication when symptoms recur.
  - NSAID usage. Consider co-prescription of a cytoprotective agent (PPI or misoprostol) in high risk individuals when the NSAID needs to be continued. If *H. pylori* positive eradicate.

#### Alarm signals:

**Family history of gastric cancer (onset <50 years), severe or persistent dyspeptic symptoms, previous peptic ulcer disease (particularly if complicated), ingestion of NSAIDs (particularly in at risk patients), unexplained weight loss, GI bleeding, anaemia, dysphagia (difficulty swallowing), coughing spells or nocturnal aspiration, protracted vomiting, palpable abdominal mass.**

H <sub>2</sub> RA:	Histamine-2 receptor antagonist (e.g. ranitidine, famotidine, cimetidine)
PPI:	Proton pump inhibitor (e.g. omeprazole, lansoprazole, pantoprazole)
GORD:	Gastro-oesophageal reflux disease
<i>H. pylori</i> :	<i>Helicobacter pylori</i>
NSAID:	Non steroidal anti-inflammatory agent (e.g. diclofenac, ibuprofen, naproxen)

## Introduction

The term dyspepsia has been used inconsistently to describe differing patterns of upper gastrointestinal symptoms. Clarity about the terminology is important. Dyspepsia and heartburn describe symptoms and are not themselves diseases. Emphasis can be given to the predominant symptom as the basis for a diagnosis (SIGN 2003).

Symptom	Description	Likely diagnosis	Approx proportion of patients
Heartburn & acid regurgitation	Burning feeling rising from the epigastrium into the chest and up towards the neck.	GORD	up to 25%
Dyspepsia	Pain or discomfort centred in the upper abdomen.	Functional dyspepsia	>50%
		Peptic ulcer	up to 25%
		Cancer	<2%

Note: This is a guide only as symptoms overlap and prevalence data varies.

The main pathological causes of dyspepsia and heartburn are gastric or duodenal ulcer and gastro-oesophageal reflux disease (GORD). People who have no definite structural or biochemical explanation for their dyspeptic symptoms are considered to have functional dyspepsia.

A minority of patients with dyspepsia will have major organic pathology e.g. oesophageal or gastric cancer. Alarm features help to identify patients who require early referral to a hospital specialist.

Functional dyspepsia is a diagnosis of exclusion. A working diagnosis of functional dyspepsia is likely to be appropriate for most patients with dyspepsia as their predominant symptom when the patient is under 50 years, there are no alarm signals, heartburn is not prominent, there are no ulcer risk factors (e.g. NSAID use, *H. pylori*) and symptoms do not indicate other organ pathology. Strictly speaking, before investigation, the general term is undifferentiated dyspepsia. Functional dyspepsia implies that other causes have been excluded usually by endoscopy. Clinical judgement must be exercised in the case of each patient to decide how much investigation is appropriate before the diagnosis may reasonably be applied.

A diagnosis of GORD may be made with high confidence for patients who describe retrosternal heartburn and/or acid regurgitation as their principal complaints. Heartburn has a 75% association with GORD (NZGG 2003). In patients with both heartburn and dyspepsia, it is preferable to treat as for heartburn first.

## Proton Pump Inhibitors

In many countries, the prescribing of proton pump inhibitors has increased steeply and correspondingly the cost has also steadily increased. Omeprazole was the single most expensive agent prescribed by New Zealand general practitioners in the year ending 30 June 2003.

The proton pump inhibitors e.g. omeprazole, lansoprazole and pantoprazole inhibit gastric acid by blocking the hydrogen-potassium adenosine triphosphatase enzyme system (the 'proton pump') of the gastric parietal cell. They are effectively pro-drugs that are converted into an active form by a high acid concentration. They are best taken 30 to 60 minutes before the first meal of the day (Yeomans 2000).

When considering the use of proton pump inhibitors it is important that they are used appropriately and they are targeted to those patients who stand to benefit the most:

- Proton pump inhibitors are not drugs of choice in the management of functional dyspepia.
- An initial short course of a proton pump inhibitor is the treatment of choice in GORD with severe symptoms; patients with endoscopically confirmed erosive, ulcerative, or stricturing oesophagitis usually need to be maintained on a proton pump inhibitor. Symptom severity and complications should always be considered when deciding on treatment options.
- Proton pump inhibitors are effective short term treatments for gastric and duodenal ulcers; they are also used in combination with antibacterials for the eradication of *Helicobacter pylori*.
- Proton pump inhibitors are used in the prevention and treatment of NSAID-associated ulcers. In patients who need to continue NSAID treatment after an ulcer has healed, the dose of proton pump inhibitor should normally not be reduced because asymptomatic ulcer deterioration may occur.
- Proton pump inhibitors may mask symptoms of gastric cancer. Particular care is required in those with alarm signals and in those over 50 years of age, the presence of gastric malignancy should be excluded before treatment.

## Functional dyspepsia

The most common type of dyspepsia encountered is functional dyspepsia, also referred to as non-ulcer dyspepsia. People with functional dyspepsia have no definite structural or biochemical explanation for their symptoms. There is no drug that has consistently been proven to be effective for functional dyspepsia (Longstreth 2003).

**Functional dyspepsia is a common condition, and no therapy is dramatically effective**  
(Moayyedi *et al* 2003).

### Principles of Management

- 1. Advice.** Reassurance and explanation are key elements in managing functional dyspepsia (Talley *et al* 2001). Patients' fears should be identified and addressed. Modification of diet (such as avoiding foods that provoke symptoms and adopting a low fat diet because high fat foods may impair gastric emptying) and stopping aggravating medications can be helpful.
- 2. Acid suppression.** A four-week trial of acid suppression may be reasonable. A small number of patients with functional dyspepsia (10%) may benefit from acid suppression therapy. A response is more likely in those with co-existent heartburn (SIGN 2003).

Proton pump inhibitors do not appear to have a significant benefit compared to H<sub>2</sub>RAs (Longstreth 2003). Meta-analyses seem to indicate an approximately 20-30% advantage for acid suppression therapy (H<sub>2</sub>RAs or PPIs) over placebo in functional dyspepsia (Nyrén 2002). However, the value of these findings may be limited due to possible publication bias and various imperfections in the studies including:

- The inclusion in studies of patients with predominant symptoms of acid reflux that is known to respond to acid suppressive treatment.
- The high placebo response to treatment (SIGN 2003).

A recent study in Chinese patients has found that patients with functional dyspepsia do not benefit from lansoprazole, a proton pump inhibitor (Wong *et al* 2002). GORD is very rare among Asians hence the inclusion of GORD patients is likely to be negligible.

It has been suggested that patients who are more likely to gain longer term benefit may have an identifiable response after only one week of treatment (SIGN 2003).

- 3. Prokinetic agents.** Prokinetic agents can occasionally help e.g. domperidone and metoclopramide, they increase lower oesophageal sphincter pressure and promote both oesophageal and gastric emptying. They are useful in those with symptoms of bloating, belching, and early satiety.

4. ***H. pylori* eradication.** The issue of whether *H. pylori* should be eradicated is controversial in patients with undifferentiated dyspepsia. It may be reasonable in symptomatic patients who have not responded to other measures, in whom no other cause can be found, after explaining the risks and the uncertain benefit of treatment. The main risks of *H. pylori* treatment include adverse reactions to the antibiotics, the selection of resistant organisms, and the development of *C. difficile* infection (Longstreth 2003).

On the basis of a meta-analysis, 9% of functional dyspepsia patients who test positive for *H. pylori* benefit from eradication. This effect can be described in terms of the number needed to treat (NNT) of 15 (i.e. 15 *H. pylori* positive functional dyspepsia patients will need to be given eradication therapy for benefit to be obtained in one (Moayyedi *et al* 2001). Other meta-analyses on the subject have found less favourable results (Laine *et al* 2001).

**Eradicating *H. pylori* infection cures functional dyspepsia in only a minority of cases.**

Many patients would therefore receive courses of antibiotics that would give them no benefit. A “test and treat” strategy is only effective in areas of moderate to high prevalence of *H. pylori* infection (>30%).

### **In Conclusion**

Not all patients with functional dyspepsia require drug treatment. However when prescription of medication is being contemplated, clinicians should appreciate there is a substantial placebo response. No drug therapies have been found to have a high success rate. Drug treatment should usually be given on a short term basis only. Where acid suppressant therapy is required H<sub>2</sub> receptor antagonists provide a reasonable option.

Separation of patients with suspected reflux disease from those with dyspepsia is important as the management needs of reflux disease patients differ substantially from those with dyspepsia.

The predominance of the presenting symptom(s) is most helpful clinically. For example, if the main complaint is a burning epigastric pain that radiates up towards the throat then this is highly predictive of gastro-oesophageal reflux disease (GORD) (Talley *et al* 2001).

**Heartburn has a 75% association with GORD**  
(NZGG 2003).

Endoscopy is a poor substitute for symptom assessment as in approximately 60% of reflux patients clear oesophagitis is absent (Dent 2002). Endoscopy is initially warranted if there is significant doubt regarding the diagnosis of GORD or if the patient relays alarm symptoms suggesting more ominous diagnoses (e.g. dysphagia, bleeding, weight loss, odynophagia).

Grades 0 to B indicate that complications are most unlikely to develop (NZGG 2003).

### Principles of Management

#### 1. Initial fast control

A trial of empiric therapy is justified in people under 50 years of age presenting with typical GORD symptoms in the absence of alarm signals (NZGG 2003).

In increasing order of potency and efficacy, the choice of drugs available includes:

- **Antacids and antacid-containing alginates** provide rapid relief of symptoms especially in those with mild disease.
- **H<sub>2</sub>-receptor antagonists** give adequate relief in many people, especially those with less severe GORD.
- **PPIs** at healing doses are recommended for severe GORD symptoms, or for proven pathology (e.g. oesophageal ulceration, Barrett's oesophagus) until symptoms have been controlled.

The optimal acute therapy for GORD is estimated and initiated based upon the patient's history. Matching the potency of therapy with disease severity can be achieved either by a "step up" approach (beginning with lifestyle and antacids and incrementally increasing the therapeutic intervention over time until symptom control is achieved) or a "step down" approach (beginning with potent agents to achieve rapid symptom control and then incrementally decreasing the intervention until break-through symptoms define the therapy necessary for continued symptom control) (Kahrilas 2003).

Once identified, the optimal acute therapy should be maintained for at least eight weeks. Further evaluation should be undertaken if the most potent medical therapy still results in a poor response (Lundell *et al* 1999, Kahrilas *et al* 1994).

The New Zealand guidelines recommend a step down approach. Patient comfort is optimised using a step down approach, with incremental changes in therapy being made at two to four week intervals (NZGG 2003).

## **2. Long term maintenance**

The management plan should acknowledge that GORD is predominantly a chronic relapsing disorder. Consequently, strategies need to be in place for long term care after achievement of initial control of reflux disease (Dent 2002).

The long-term management of GORD has been dominated by daily maintenance treatment with PPIs to prevent relapse (Bardhan 2003). This may not be necessary in all patients; the most suitable option will need to be determined in conjunction with the patient and may be one of a few options including:

1. Continuous (*daily use of lowest effective medication*)
2. Intermittent (*short course of medications when symptoms occur*)
3. On-demand (*one-dose when symptoms occur*)

If acute medical therapy alleviates symptoms, patients with less severe disease (Grades 0,A and B) can be given a trial off medication. The need for maintenance medical therapy is determined by the rapidity of recurrence. Recurrent symptoms in less than three months suggests GORD is best managed with continuous therapy, while remissions longer than three months can be adequately managed by repeated courses of acute therapy as necessary (Kahrilas 2003).

The three-month figure is derived from observations of patients randomised to placebo in maintenance trials of proton pump inhibitors. If recurrence were going to occur within one year, it invariably occurred within the first three months. In one trial, for example, 76% of patients treated with placebo were recurrent at one year; 55% (72% of the recurrences) developed within the first month (Robinson 1996).

In endoscopy negative patients, or those with only mild oesophagitis (Grades 0, A or B), intermittent courses of therapy or day to day symptom driven use of medication (on-demand use), frequently succeed, with substantial reduction of the costs of medication (Dent 2002).

Endoscopy is not routinely indicated in people with typical symptoms that respond to treatment. It should be considered, however, in people who are *Helicobacter pylori* positive if underlying ulcer disease is suspected, and those with persistent or poorly controlled symptoms, especially if maintenance proton-pump inhibitor treatment is being considered (Prodigy 2001).

### 3. Tailoring the dose to the individual

Reduction of the intensity of daily therapy by stepping down the dose or therapeutic agent is the traditional approach.

*Once daily PPI is sufficient for most patients*

It has been shown that the proportion of patients prescribed greater than single dose PPI is as high as 30% (Inadomi 2003).

**Scale of potency: in descending order of 'acid suppression'**

- PPIs
- H<sub>2</sub>RAs
- Antacids or alginates
- Lifestyle & Diet

Although the plasma half-lives of PPIs are quite short, their mechanism of action enables most patients to be satisfactorily treated with once daily dosing. Generally it does not matter whether the dose is given in the morning or the evening. However, acid secretion recovers faster in some patients than others and it may be worth experimenting with switching the dose to the evening. This may benefit patients with reflux whose nocturnal symptoms are not relieved when the PPI is given in the morning. About 10-20% of patients with severe reflux disease will get better relief of symptoms with a twice daily dose (Yeomans 2000).

A study was conducted to determine whether patients requiring greater than single dose PPI for initial symptom resolution could be stepped down to single dose PPI. A total of 117 subjects enrolled in the study, all were followed to the primary endpoint. 79.5% did not report recurrent symptoms of heartburn or acid regurgitation during the 6 months after step down to single dose PPI (either omeprazole 20mg or lansoprazole 30mg per day). The patients also received education regarding lifestyle modifications (Inadomi 2003).

**Most patients who are asymptomatic on twice daily PPI (e.g. omeprazole 20mg twice daily) can be successfully stepped down to once daily PPI (i.e. omeprazole 20mg daily).**

### *Lowest effective PPI dose*

After healing has been achieved, the dose should be stepped down to the lowest dose that maintains control of symptoms. A regular maintenance low dose of most PPIs (e.g. omeprazole 10mg daily) will prevent recurrent GORD symptoms, and should be used in preference to the higher healing dose. Where necessary, should symptoms reappear, the higher dose should be recommenced.

Omeprazole 20mg given on alternate days may also be an effective option in some patients (Wilde & McTavish 1994).

In severe, complicated (stricture, ulcer, haemorrhage) or Barrett's oesophagitis the full dose should be maintained.

**Healing or full-dose PPIs:** omeprazole 20mg, lansoprazole 30mg, pantoprazole 40mg daily  
**Low or half-dose PPIs:** omeprazole 10mg, lansoprazole 15mg, pantoprazole 20mg

### *Intermittent and on-demand use of therapy*

Intermittent or on-demand therapy probably approximates more closely how most patients use medication for reflux disease. Both the use of short courses of continuous therapy (intermittent therapy) or dosing on a day to day basis according to symptom status (on-demand therapy) have been shown to be effective and acceptable to patients, and to result overall in at least halving the amount of medication consumed compared to continuous therapy (Dent 2002).

### *Intermittent Therapy*

Treatment is started when symptoms recur during a relapse and is stopped when the patient becomes asymptomatic once again. Treatment blocks are typically 2-4 weeks at the dose effective for the initial control. The patient then remains off therapy until the next attack (Kahrilas 2003).

A randomised trial showed that only half of patients who have their symptoms healed need ongoing treatment (Bardhan 1999). The trial included 677 patients with mild to moderate heartburn and a normal endoscopy or only mild erosive changes. Patients were randomly assigned to omeprazole (10 or 20mg/day) or ranitidine (150mg twice daily). After two weeks, asymptomatic patients were given no further therapy unless symptoms returned upon which they were treated for two to four weeks with the drug that initially caused remission. At the end of one year, approximately 50% of patients in all three treatment groups had not required medication for at least six months (Bardhan 1999).

### *On-Demand treatment*

On-demand treatment is a logical alternative to intermittent therapy, instead of blocks of treatment of fixed duration, drugs are taken only when symptoms recur and are continued until they are relieved (Bardhan 2003).

It is common for patients with mild disease and infrequent symptom relapses to use a PPI only on demand. Patients with symptomatic or mild erosive GORD are therefore ideal for on-demand or intermittent treatment (Bardhan 2003).

The threshold for use of continuous PPIs as opposed to on-demand or intermittent therapy depends on the impact of GORD on quality of life, the severity of GORD and cost.

### **In conclusion**

1. It is important to gain healing as quickly as possible after a relapse.
2. Approximately half the patients with less severe disease can be controlled on intermittent or on-demand therapy.
3. For those patients who require maintenance therapy aim for the lowest effective dose. Low dose PPIs include omeprazole 10mg, lansoprazole 15mg and pantoprazole 20mg daily.

## Helicobacter pylori infection

*Helicobacter pylori* is a Gram negative flagellated spiral bacterium found in the stomach. Infection with *H. pylori* is predominantly acquired in childhood. The organism is associated with lifelong chronic gastritis and may cause other gastroduodenal disorders.

*H. pylori* prevalence rates vary with year of birth and social class in the developed world. Prevalence rates in many developed countries tend to be much higher (50-80%) in individuals born before 1950 compared with rates (<20%) in individuals born more recently (Harvey *et al* 2002). In many developing countries, the infection has a high prevalence (80-95%) irrespective of the period of birth (Axon 1993).

Adult prevalence is believed to represent the persistence of a historically higher rate of infection acquired in childhood, rather than increasing acquisition of infection during life.

Prevalence of *H. pylori* infection is very variable among various population groups in New Zealand. Detailed data relating to prevalence around New Zealand are limited, but Dunedin and Christchurch population-based studies suggest that prevalence in the central and southern South Island is similarly low (<30%). While Auckland data suggests that rates vary according to age and ethnicity, with adults between 40-65 years having high rates (>30%) for all groups (European, Maori and Pacific people) (NZGG 2003).

The effects of eradication treatments for <i>Helicobacter pylori</i>	
<b>Beneficial</b>	<i>H. pylori</i> eradication for healing and preventing recurrence of both duodenal and gastric ulcer
<b>Small benefit</b>	<i>H. pylori</i> eradication for functional dyspepsia
<b>Unlikely to be beneficial</b>	<i>H. pylori</i> eradication in people with gastro-oesophageal reflux disease

(Adapted from Delaney *et al* 2003)

## Peptic Ulcer

Many textbooks suggest that symptoms can accurately identify peptic ulcer disease. Unfortunately, classic ulcer symptoms (such as postprandial epigastric pain or night pain) often occur in patients with functional dyspepsia, and many patients with an ulcer have atypical complaints (Talley 2001).

Endoscopy remains the test of choice to rule out chronic peptic ulceration, however it can be inferred by indirect testing. *Helicobacter pylori* causes 90% of duodenal ulcers and 70% of gastric ulcers; aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) account for most of the remainder. Patients who are not infected with *H. pylori* and not taking NSAIDs have a very low probability of ulcer disease (Talley 2001).

The New Zealand guidelines recommend that in areas of moderate to high prevalence of *H. pylori* infection (>30%) and high incidence of symptomatic peptic ulceration the 'test-and-treat' strategy may be used in a person under 50 years with no alarm signals. The test-and-treat strategy should not be relied on in areas of low prevalence (<30%) (NZGG 2003).

Eradication of *Helicobacter pylori* is the mainstay of the management of peptic ulcer disease. Continued maintenance therapy after successful eradication should only be required in a minority of patients. According to a meta-analysis by Hopkins *et al*, after eradication of associated *H. pylori* infection, duodenal ulcer recurrence at one to four years is about 6% and the recurrence rate of gastric ulcers at one to four years is approximately 4% (Hopkins 1996).

Proton pump inhibitors have a role in the eradication of *H. pylori* and are components of the majority of gold standard regimens. Eradication rates of up to 90% have been achieved when combining a proton pump inhibitor with two antibiotics for one week. There are two eradication regimens subsidised in New Zealand (see table).

Eradication Regimen	Brand Name	Duration	Subsidy
Omeprazole 20mg bd Amoxicillin 500mg, two bd Clarithromycin 500mg bd	Klacid Hp7 Losec Hp7 OAC	7 days	\$58
Omeprazole 40mg daily Amoxicillin 500mg tds Metronidazole 400mg tds	Helicosec	7days	\$58

(Pharmaceutical Schedule December 2003).

Peptic ulcers should need no further treatment once successful eradication has been completed.

Maintenance treatment with a proton pump inhibitor or H<sub>2</sub>RA should only be required in a minority of patients including those with a history of complications, significant co-morbidity, or who have frequent recurrence.

## NSAIDs

NSAIDs are significantly associated with dyspepsia and peptic ulcer. At initial presentation the drug history of all patients should be reviewed (NZGG 2003).

There are generally three levels of adverse effects with NSAIDs. The first includes dyspepsia symptoms, the second the development of intestinal mucosal abnormalities including peptic ulceration, and the third ulcer complications (predominantly bleeding and perforation). Unfortunately, ulcers and/or their complications are not necessarily preceded by dyspepsia; not infrequently complications occur in otherwise asymptomatic individuals (NZGG 2003).

**NSAID-induced ulcers are more likely to be gastric than duodenal and are often asymptomatic until complications occur.**

Endoscopically verified ulcers can be documented in up to 40% of chronic NSAID users, but it is estimated that as many as 85% of these never become clinically apparent (Rostom *et al* 2000). The estimated annual incidence of a serious gastrointestinal complication (perforation, obstruction or bleeding) with a traditional NSAID is around 1.4% (NPS 2001).

### **Risk factors for NSAID associated adverse upper GI events (NZGG 2003).**

Use of NSAID (includes aspirin and COX-2 inhibitors alone or in combination) plus the following:

- aged >65 years
- history of peptic ulcer
- history of upper GI bleeding
- concomitant disease, especially coronary heart disease
- increased frailty such as substantial arthritis-related disorder (OA is a milder disease than RA and requires lower doses of NSAID; in addition, oral prednisone is rarely used in osteoarthritis)
- previous NSAID gastropathy
- concomitant use of corticosteroids
- concomitant use of anticoagulants
- concomitant use of biphosphonates
- high doses of NSAID (includes NSAID + aspirin)
- *H. pylori* infection

**Increased-risk individuals are:**  
*aged <65 yrs with 2 risk factors*  
*aged >65 yrs with 1 risk factor.*

Co-prescription of gastro-protective agents with traditional NSAIDs or aspirin in high risk individuals is recommended for those over 65 years old with one additional risk factor, or those under 65 years old with two or more risk factors (NZGG 2003). Proton pump inhibitors are better tolerated than misoprostol. Proton pump inhibitors can be used at standard doses e.g. omeprazole 20mg daily. H<sub>2</sub>RAs at standard doses (e.g. ranitidine 150mg twice daily) cannot be recommended as they are not effective in preventing gastric ulcers. There is no evidence to justify the simultaneous use of gastro-protective drugs with COX-2 inhibitors.

Gastro-intestinal side effects of NSAIDs are dose dependent therefore if the NSAID cannot be stopped, it is important to keep the dose as low as possible.

Epidemiological studies suggest that reducing NSAID doses reduces risk, possibly to background levels with ibuprofen =1200mg per day (Hawkey & Langman 2003).

**Dose dependent risks for paracetamol and selected NSAIDs for upper gastrointestinal bleeding.**

Variable	Daily dose (mg)	OR (95% CI)
Paracetamol	< 2000	1.2 (1.0, 1.4)
	2000-3999	1.2 (0.8, 1.7)
	≥ 4000	1.0 (0.5, 1.9)
Ibuprofen	< 1200	1.1 (0.6, 2.0)
	1200-1799	1.8 (0.8, 3.7)
	≥ 1800	4.6 (0.9, 22.3)
Diclofenac	< 75	2.2 (0.8, 5.8)
	75-149	3.2 (1.9, 5.5)
	≥ 150	12.2 (5.6, 26.7)
Piroxicam	≤ 10	9.0 (2.1, 39.2)
	11-20	12.0 (6.5, 22.1)
	≥ 21	79.0 (9.9, 931.8)

OR (95% CI), odds ratio (95% Confidence Interval).  
 Data are based on reported doses used in the week prior to presentation, and are adjusted for use of aspirin, ketoprofen, anticoagulants, smoking, and past history of upper gastro-intestinal problems. (Hawkey & Langman 2003).

Increasing NSAID dosage within the accepted ranges approximately triples the risk of ulcer complications. The possibility that ibuprofen at doses =1200mg a day may offer acceptable safety, especially when combined with a proton pump inhibitor for defined patients, warrants formal evaluation (Hawkey & Langman 2003).

**COX-2 Inhibitors**

- COX-2 inhibitors are no more effective than conventional NSAIDs.
- The absolute reduction in serious gastro-intestinal complications with COX-2 inhibitors is small.

In high risk groups (i.e. baseline risk of a gastro-intestinal complication ≥ 10% in any one year), the number needed to treat with a COX-2 inhibitor to prevent one gastro-intestinal complication is in the region of 10-20. This increases to 100-200 for typical patients (i.e. baseline risk about 2% per year) and may be as high as 500 for low risk patients (MacRae *et al* 2004).

COX-2 inhibitors can be used in preference to standard NSAIDs when there is a clear indication, for example in those patients at high risk of developing serious gastro-intestinal side effects. Even in these patients the use of COX-2 inhibitors should be considered very carefully (NICE 2001).

As with the traditional NSAIDs it is reasonable to initiate therapy at the lowest dose, adjusting as needed to the minimum effective dose.

**If you choose a COX-2 selective NSAID always start at the lowest dose and modify according to response.**

Although the usual recommended dose for celecoxib in patients with osteoarthritis is 200mg daily, symptomatic improvement (relative to placebo) has been shown in patients taking 100mg daily (Bensen 1999). The efficacy of this lower dose is particularly relevant as almost 30% of the study population was older than 70 years of age; this reinforces the notion that reduced doses of NSAIDs can be effective especially in the elderly (NPS 2001).

There is no evidence to justify the simultaneous use of gastro-protective drugs with COX-2 inhibitors as a means of further reducing potential gastro-intestinal side effects (BNF 2003).

### **Low dose aspirin**

Low dose aspirin will contribute to gastro-intestinal toxicity even when taken as an enteric coated tablet.

Low dose aspirin combined with a COX-2 inhibitor will reduce the gastro-intestinal benefit of the COX-2 inhibitor. Additionally research has suggested that COX-2 inhibitors should be avoided in patients with cardiovascular disease due to an increase in myocardial infarctions (Bombardier 2000).

If low dose aspirin is required in combination with an anti-inflammatory agent, and the patient is at high risk of serious gastro-intestinal side effects, choose the least gastro-toxic traditional NSAID at the lowest effective dose and consider the use of a gastro-protective agent e.g. omeprazole 20mg daily.

### **In conclusion**

It is likely that an overall reduction in NSAID toxicity will only be achieved by applying different strategies to different patients. Protective strategies include either co-prescription of a protective drug such as a proton pump inhibitor or misoprostol with a traditional NSAID, or substitution of a drug with reduced toxicity such as a COX-2 inhibitor. Regardless of the anti-inflammatory agent chosen it is important to use the lowest effective dose of the anti-inflammatory agent.

## Quick Reference Charts

### Alarm signals (NZGG 2003)

The following symptoms and signs tend to indicate the presence of significant organic disease:

- family history of gastric cancer (onset <50 years)
- severe or persistent dyspeptic symptoms
- previous peptic ulcer disease, particularly if complicated
- ingestion of NSAIDs, particularly in older patients
- unexplained weight loss
- GI bleeding
- anaemia
- dysphagia (difficulty swallowing)
- coughing spells or nocturnal aspiration
- protracted vomiting
- palpable abdominal mass.

*NB: All symptoms should be regarded as more serious in patients who are over the age of 50 when presenting for the first time. Gastric cancer tends to occur a decade earlier in patients of Maori, Pacific Island or Asian origin.*

### Information for patients with functional dyspepsia (SIGN 2003)

When a diagnosis of functional dyspepsia has been made, it may be helpful to explain to patients that:

- No disease or abnormality has been found and that this should be taken as reassuring.
- Functional dyspepsia is very common and is not itself serious, though the discomfort, pain, distention and fullness which are perfectly genuine, are often unpleasant and bothersome.
- The definitive causes of functional dyspepsia are not known. It is known that, when compared with asymptomatic individuals, the stomach in many patients with functional dyspepsia empties more slowly after meals. There is also evidence of heightened visceral sensation in many functional dyspepsia patients who experience discomfort when the stomach is distended to a degree that does not cause discomfort in healthy subjects.
- Functional dyspepsia is not a condition caused by gastric hypersecretion: acid secretion is usually normal.
- Functional dyspepsia is not usually caused by stress, anxiety or depression but these factors may worsen the symptoms and diminish a patient's ability to cope with them.
- Functional dyspepsia is not caused by sensitivity or allergy to dietary constituents. However functional dyspepsia sufferers, like anyone else, should avoid foods that upset them.
- Drug treatment is not very effective in functional dyspepsia but a minority of patients are helped by some medications.

### Los Angeles endoscopic classifications of GORD (NZGG 2003)

Grade	Findings
0	Normal endoscopic findings
A	One or more mucosal breaks no longer than 5mm, none of which extends between the tops of mucosal folds
B	One or more mucosal breaks more than 5mm long, none of which extends between the tops of mucosal folds
C	Mucosal breaks that extend between the tops of two or more mucosal folds but which involve less than 75% of the oesophageal circumference
D	Mucosal breaks that involve at least 75% of the oesophageal circumference

In approximately 60% of reflux patients clear oesophagitis is absent (Dent 2002).

### Patient description of “heartburn” symptoms

Heartburn has a 75% association with GORD. The word “heartburn” is poorly understood by patients: instead the cardinal symptom of reflux disease is recognised better if it is described in simple words. It is likely that the use of short self administered questionnaires in routine clinical care will improve the reliability of separation of reflux induced symptoms from true dyspepsia (Dent 2002a).

Which one of these four statements BEST describes the main discomfort you get in your stomach or chest?

- A burning feeling rising from your stomach or lower chest up towards your neck.
- Feelings of sickness or nausea.
- Pain in the middle of your chest when you swallow.
- None of the above, please describe below.

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### General measures for people with GORD (Prodigy 2001)

- **Lifestyle modifications** may be useful for oesophageal related problems, although the evidence for their effectiveness is limited. Smoking cessation; weight loss in obese people; propping up the bed head; and avoiding provoking factors including bending, alcohol, coffee, and fatty foods may help. Other suggestions include eating smaller meals, not eating before bed, and wearing looser clothing.
- **Aspirin and nonsteroidal anti-inflammatory drug (NSAID) use** should be discouraged.
- **Consider withdrawing medication that may adversely affect the lower oesophageal sphincter**, e.g. theophylline, nitrates, and calcium-channel blockers.
- **Anxiety regarding symptoms should be addressed.** People who consult with dyspepsia are often more anxious about the significance of their symptoms than those who do not, but the symptoms are not generally more severe or long-lasting.

### Drugs most likely to cause dyspepsia (Talley *et al* 2001)

NSAIDs	Levodopa
Digoxin	Theophylline
Antibiotics (macrolides, metronidazole)	Quinidine
Corticosteroids, oestrogens	Niacin
Iron	Gemfibrozil
Potassium chloride	Colchicine

### Drug Induced oesophagitis (Castell 2003)

The types of medication causing direct oesophageal injury can be roughly divided into antibiotics, anti-inflammatory agents, and others.

- Tetracyclines are the most common antibiotics to induce oesophagitis, particularly doxycycline.
- Essentially all of the anti-inflammatory agents can damage the oesophagus; including aspirin, traditional NSAIDs and COX-2 Inhibitors.
- The major offenders in the "other" category include potassium chloride, quinidine preparations, and iron compounds. In addition, the bisphosphonate alendronate is likely to become an important cause because of its increasing use for the treatment of osteoporosis and other disorders.

To minimise oesophageal injury:

- Medication should be taken with a full glass of water (~240ml) to minimise the risk of the tablet getting stuck in the oesophagus and causing local erosions.
- Stand or sit upright for at least 30 minutes. Avoid lying down after taking medication.
- Take the medication with food.

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