

## Proton pump inhibitors

About 1 in 6 Australians have consulted a GP for dyspepsia, according to survey data.<sup>1</sup> In 2004–5, 75% of first presentations with reflux resulted in a proton pump inhibitor (PPI) prescription\*; the volume of PBS prescriptions for PPIs in the same period was around 1 million per month.<sup>2</sup>

### Steps to stepping down PPI therapy

After initial PPI therapy for gastro-oesophageal reflux disease (GORD) or uninvestigated dyspepsia, guidelines recommend the 'step-down' approach for symptom control.<sup>3–5</sup> Many GPs are aware of the step-down strategy, but it does not appear to be used widely. In 2004–5, two-thirds of PPI prescriptions were for the maximum number of repeats\* and only 1 in 10 was for a low-dose preparation.<sup>2</sup> The 3 steps to step-down PPI therapy are:

#### 1. Prescribe no more than one repeat initially

An initial 4-week course of standard-dose PPI (see Table 1, page 2, for doses) is appropriate, either as empirical therapy if alarm symptoms are absent (see Box, page 3) or if ulcer, malignancy and severe oesophagitis have been ruled out by endoscopy.<sup>5</sup> Ask the patient to return for review if symptoms persist or recur. After discontinuation, 20–40% of patients will not require another PPI prescription for 6–12 months.<sup>5</sup> In endoscopy-confirmed oesophagitis, healing rates are increased from about 75% to around 90% if therapy is extended to 8 weeks.<sup>5</sup> If symptomatic oesophagitis persists, a further 4 weeks of double-dose therapy is indicated.

In the minority of patients with severe or complicated oesophagitis, continuous standard-dose therapy is indicated.

#### 2. Discuss intermittent, symptom-driven maintenance therapy

A study of 46 650 patients in UK general practice suggests that most of those receiving PPIs for any indication took their treatment when required, not continuously as prescribed.<sup>6</sup> Trials indicate that patient satisfaction with intermittent, symptom-driven maintenance therapy in non-erosive and mild erosive GORD is high and similar to that with continuous therapy<sup>7–9</sup>, although in one trial the endoscopic relapse rate was higher.<sup>9</sup>

#### 3. Prescribe low-dose maintenance therapy

If continuous maintenance therapy is needed, step down to a low-dose PPI (see Table 1, page 2). Low doses control symptoms in most cases: 9 patients with healed oesophagitis would need to be treated with a standard dose rather than a low-dose PPI to avoid 1 additional relapse over 6–12 months.<sup>10</sup> Return to a standard dose if symptoms are not controlled or in case of relapse. There is no evidence that double-dose PPIs are more effective than standard dose in maintenance of healed oesophagitis<sup>10</sup>, but a few patients may require titration to a high dose to control symptoms.

#### Test for and treat *Helicobacter pylori* infection

Testing for *Helicobacter pylori* infection and treating with triple therapy is an option in uninvestigated dyspepsia, either first line or if initial PPI therapy fails. In 2 trials in dyspeptic *H. pylori*-positive patients, the average proportion of patients with no or minimal symptoms at 12 months was 60% for eradication therapy compared with 47% for short-term PPI acid suppression.<sup>5</sup> In patients with non-ulcer dyspepsia proven by endoscopy, eradicating *H. pylori* had a smaller effect, curing dyspeptic symptoms in around 1 patient in 18 at 3–12 months of follow-up.<sup>11</sup> There is no evidence that eradication improves symptoms for people with confirmed GORD.<sup>5</sup>

\* Source: BEACH data, Australian General Practice Statistics and Classification Centre, a collaborating unit of the Family Medicine Research Centre, University of Sydney and the Australian Institute of Health and Welfare.

## Counselling people with dyspepsia in community pharmacy<sup>5,12</sup>

<b>Ask about alarm signs</b>	If any <b>alarm sign</b> is present (see Box, right), <b>advise patient to see a GP</b>
<b>Ask about duration of symptoms and self-care</b>	<b>Advise patient to see a GP</b> if symptoms are: <ul style="list-style-type: none"> <li>• <b>non-resolving</b> despite therapy</li> <li>• <b>severe</b> (interfering with normal activities)</li> <li>• <b>frequent</b> (&gt; 2 days/week) or</li> <li>• <b>recurrent</b> (within 5 days of spontaneous recovery or stopping treatment)</li> </ul>
<b>Ask about medications that may cause dyspepsia</b>	If patient is taking calcium-channel blockers, dopaminergic agents, anticholinergics, nitrates, theophylline, bisphosphonates, oral corticosteroids, tetracyclines, iron, potassium chloride or prescription NSAIDs, <b>advise them to see a GP</b>
<b>Offer lifestyle advice</b>	Advise about lifestyle changes for general health benefits and avoidance of dyspepsia triggers
<b>Offer over-the-counter medication for symptom relief</b>	An antacid/alginate or an H <sub>2</sub> antagonist, i.e. famotidine (Pepzan) or ranitidine (Gavilast, Ranitic, Ranoxyl, Ultac, Zantac), is appropriate for mild or intermittent symptoms

## Lesser-known adverse effects of PPIs

### Can PPIs increase the risk of infection?

Observational studies have found a 2–3-fold increase in risk of *Clostridium difficile* infection in patients using a PPI.<sup>13–15</sup> *C. difficile* is more often seen in hospitals; the rate of *C. difficile*-associated diarrhoea in a recent Western Australian hospital study was about 1 per 1000 hospital discharges<sup>16</sup>, while the diagnosis rate in a study in UK general practice was 22 cases per 100 000 patients in 2004.<sup>13</sup>

The possibility of *C. difficile* infection may be reason to review PPI therapy in high-risk patients before admission to hospital. Risk factors for *C. difficile* infection include using antibiotics, age ≥ 75 years and renal failure.<sup>13–15</sup> *C. difficile* infection should be distinguished from the symptoms of diarrhoea that occur at a rate of around 5–15 per 100 patient-years of PPI use<sup>17,18</sup>, and from the uncommon cases of microscopic colitis that appear to be specifically associated with lansoprazole.<sup>19</sup>

### Interstitial nephritis: a rare but serious adverse effect of PPIs

Acute interstitial nephritis is a rare but serious hypersensitivity reaction that has been reported with all PPIs. Although only about 30 cases have been reported in Australia, PPIs are now the most common cause of drug-induced interstitial nephritis treated in hospital renal units.<sup>20–22</sup> Renal function typically improves after withdrawal of the PPI, but not in all cases.<sup>20</sup>

The symptoms of PPI-related interstitial nephritis are non-specific (e.g. weight loss, malaise, fever and nausea).<sup>20</sup> Case reports describe an onset as soon as 12 days or as late as 12 months after starting PPI therapy.<sup>20</sup> If a patient taking a PPI becomes unwell without identified cause, assess renal function by serum creatinine and urine dipstick (blood and protein) tests. In cases of renal impairment, refer to a nephrologist or stop the PPI and review. Interstitial nephritis may be asymptomatic and diagnosis can only be confirmed by renal biopsy.<sup>20</sup>

**Table 1: Standard and low doses of PPIs<sup>3</sup>**

PPI	Standard dose <sup>†</sup>	Low dose <sup>†</sup>
esomeprazole Nexium	20 mg daily*	20 mg daily
lansoprazole Zoton	30 mg daily	15 mg daily
omeprazole Acimax, Losec, Meprozol, Omepral, Probitor	20 mg daily	10 mg daily <sup>‡</sup>
pantoprazole Somac	40 mg daily	20 mg daily
rabeprazole Pariet	20 mg daily	10 mg daily

<sup>†</sup> Standard dose refers to the dose usually recommended for initial therapy in uninvestigated dyspepsia, GORD, or oesophagitis; low dose refers to the lower dose recommended for maintenance therapy.

\* 40 mg daily is indicated for erosive reflux oesophagitis.

‡ Losec tablets are the only brand of omeprazole available in a 10 mg strength.



## Co-prescribing an NSAID and a PPI: Does it make sense?

Peptic ulcer is a well-known risk of NSAID use. While 10–20% of people taking an NSAID experience dyspepsia, these symptoms rarely predict serious gastrointestinal complications.<sup>23</sup> In osteoarthritis patients with few risk factors for ulcer, the risk of experiencing a perforation, obstruction or bleed as a complication of NSAID-induced ulcer is about 1 per 100 patient-years of use.<sup>24</sup>

### Stop or reduce NSAID use to prevent ulcers

Stopping or reducing the dose of NSAIDs is the most effective way to avoid ulcers.<sup>3</sup> Paracetamol has a superior safety profile to that of NSAIDs and is first line in musculoskeletal pain.<sup>25</sup> Discuss the potential harms of NSAIDs with patients, and review the need for ongoing treatment at least every 6 months.<sup>5</sup>

When the benefits of using an NSAID outweigh the possible harm of causing ulcer complications:

- Use the lowest dose of the NSAID for the shortest time or use intermittent therapy (except low-dose aspirin for cardiovascular protection, which must be taken continuously).
- Combine the NSAID with paracetamol to enable a lower dose of the NSAID to be used.<sup>4</sup>
- Use an NSAID known to have a lower gastrointestinal risk, such as diclofenac or ibuprofen (maximum 1200 mg daily), in preference to higher-risk agents such as piroxicam or ketoprofen.<sup>4,5</sup>

### Alarm signs — indications for urgent\* endoscopy<sup>5</sup>

- Vomiting blood or blood in faeces (**same day referral** if significant acute bleeding)
- Difficulty or pain on swallowing
- Unexplained weight loss
- Upper abdominal mass
- Persistent vomiting

\* National Institute for Clinical Excellence guidelines recommend investigation within 2 weeks, except in acute cases.<sup>5</sup>

### Options for gastroprotection

Consider gastroprotective strategies only for patients at increased risk of ulcer complications; for others the benefit is small compared with the added cost and potential harm. Age  $\geq$  65 years, use of anticoagulants or oral corticosteroids, and serious comorbidity can all increase the risk of ulcer complications.<sup>23</sup> Patients with a history of ulcer are at the greatest risk.<sup>26</sup> In those starting NSAID therapy with dyspepsia or a history of ulcer, testing for, and eradicating, *H. pylori* may be a worthwhile additional measure to reduce the risk of ulcer.<sup>27</sup>

It is not known which gastroprotective strategy is most effective. In patients with a recent history of gastric or duodenal ulcer complications, rates of recurrent bleeding ulcer were equally high (5% in 6 months) with either celecoxib or the combination of naproxen or diclofenac and a PPI.<sup>28,29</sup>

### PPI or double-dose H<sub>2</sub> antagonist?

Co-prescribing a PPI or double-dose H<sub>2</sub> antagonist with a conventional NSAID prevents endoscopically detectable gastric and duodenal ulcers<sup>30</sup> and is recommended by some guidelines<sup>3,4</sup>, but no trials have assessed if these strategies prevent ulcer complications. PPIs also reduce NSAID-related dyspepsia and are better tolerated than misoprostol<sup>30</sup>; however, the PBS restricted benefit for PPIs does not include gastroprotection.

### Misoprostol

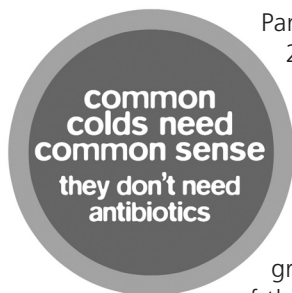
Misoprostol 800 micrograms daily was shown in one large trial to reduce the incidence of serious NSAID-related ulcer complications from 0.74% to 0.36% over 6 months, but it caused an extra 1 in 14 patients to withdraw because of adverse effects such as diarrhoea and nausea.<sup>31</sup> Misoprostol is a PBS authority item for reducing NSAID gastrointestinal complications in patients with a history of ulcer complications. Misoprostol must not be used in pregnancy.

### COX-2 selective NSAIDs

COX-2 selective NSAIDs may cause fewer ulcer complications than conventional NSAIDs (see *NPS RADAR, Aug 05: Elevated cardiovascular risk with NSAIDs?*). Concomitant low-dose aspirin eliminates any gastrointestinal safety advantage of COX-2 selective NSAIDs.<sup>4</sup> It has not been established if the combination of a COX-2 selective NSAID and a PPI results in fewer ulcers than the combination of a conventional NSAID and a PPI, but in 1 trial in patients with risk factors for ulcer, co-prescribing a COX-2 selective NSAID and esomeprazole reduced the incidence of endoscopically detectable ulcers compared with a COX-2 alone.<sup>32</sup>

## Common colds need common sense, they don't need antibiotics

Twenty-five per cent of Australians incorrectly believe that antibiotics can treat a common cold. This is the sixth winter that NPS is promoting the appropriate use of antibiotics through the *common colds need common sense, they don't need antibiotics* campaign.



Parents and carers of children aged 2–5 years continue to be the main focus, as they visit doctors for generalised upper respiratory tract infections more than any other group. Evaluation from last year showed awareness of the campaign among this target group to be more than twice that of the total community, and only 17% had incorrect beliefs about the role of antibiotics for colds. This was achieved through our multi-level approach working with general practice, community pharmacy, children's services, community groups and health centres across Australia.

NPS is again encouraging general practitioners and pharmacists to participate in the campaign. Materials to help with patient education will be sent in June. The campaign uses Harvey the wombat to show that antibiotics are not needed for children's colds. The latest book is *Harvey catches a cold and visits the doctor*. We hope that making this book available for parents to read to their child in general practice patient waiting areas will help GPs negotiate antibiotic use with parents and carers of younger patients.

Child care services and public libraries will receive a copy of the book this year.

Order additional resources from the campaign website at [www.nps.org.au/consumers](http://www.nps.org.au/consumers) (follow the links), where you can find more information, materials and an online version of the book.



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