



National Prescribing Service Limited

**Case study 57 report:  
Proton pump inhibitors —  
appropriate and safe use**



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# Case study 57

## Proton pump inhibitors — appropriate and safe use

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### Scenario

Mr Lee is a 60-year-old patient who has just finished his last omeprazole tablet. One year ago he presented complaining of an intermittent burning sensation in the epigastric region of his abdomen. He was diagnosed with gastro-oesophageal reflux disease and started on omeprazole 20 mg daily. Six months later, Mr Lee was symptom free and omeprazole was discontinued. However, Mr Lee returned two weeks later complaining of similar discomfort. He was referred for an endoscopy but the results were unremarkable. He was restarted on omeprazole 20 mg daily and has been taking it since then. He has been symptom free for the past five and a half months. He denies any episodes of gastrointestinal bleeding, difficulty in swallowing or weight loss.

He smokes a pack of cigarettes a day and drinks on weekends and at social functions. He also uses irbesartan 300 mg/hydrochlorothiazide 12.5 mg daily for his hypertension, which is well-controlled. He has no history of renal or hepatic disease and no known drug allergies. His father has diabetic nephropathy. The rest of his family history is unremarkable.

On examination he was afebrile and his blood pressure was 126/80 mmHg. He has a body mass index of 28 kg/m<sup>2</sup>. There were no other significant findings.

1. a) Would you recommend that Mr Lee continue using a proton pump inhibitor (PPI) (e.g. omeprazole)?

Yes       No

Why/why not? \_\_\_\_\_

b) If you recommend continuation of PPI therapy AND/OR would like to recommend another medication instead of a PPI, specify:

regularly

as required

\_\_\_\_\_

c) If Mr Lee continues to remain asymptomatic at the next review after following the regimen you specified in 1b, would you:

continue the regimen as above

change the medication/ regimen (please specify) \_\_\_\_\_

stop the medication

What is the reason for your decision above?

\_\_\_\_\_

2. Mr Lee read that PPIs could cause rare but serious side effects.

a) In patients using PPIs, list three potential rare but serious adverse events.

- i. \_\_\_\_\_
- ii. \_\_\_\_\_
- iii. \_\_\_\_\_

b) Because of his father's nephropathy Mr Lee is very concerned about possible serious kidney problems from using a PPI. How would you respond to his concerns?

\_\_\_\_\_

3. Mr Lee was advised to stop smoking and reduce his weight and alcohol intake a year ago, to see if these contributed to his heartburn symptoms. Nonetheless he found it difficult to make these lifestyle changes. What practical advice can you give to patients such as Mr Lee to help them adhere to lifestyle advice?

- i. \_\_\_\_\_
- ii. \_\_\_\_\_
- iii. \_\_\_\_\_

# Summary of results

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At the time of publication, 234 responses were received. This report summarises the responses to questions in case study 57: Proton Pump Inhibitors (PPIs) – appropriate and safe use from 100 health professionals (including 76 general practitioners).

## Case synopsis

Mr Lee is a 60-year-old patient who has been taking omeprazole 20 mg for the past year for symptoms of intermittent burning sensation in the epigastric region. He has been symptom free for the past five and a half months. His current BP is 126/80 mmHg and BMI is 28 kg/m<sup>2</sup>. His endoscopy results six months ago were unremarkable. He is an active smoker and social drinker. His past and family history is unremarkable. (See page 3 for more details.)

## Continuing PPI therapy

- 67% of respondents would continue PPI therapy for Mr Lee whereas 33% would discontinue its use. 12 respondents who would discontinue PPI would not recommend any drug therapy.
- The two main reasons for continuing PPI therapy were symptom control (38.8%) and to reduce the possibility of recurring symptoms (37.3%). Main reasons for discontinuing PPI therapy were that Mr Lee had been symptom free for over 5 months (72.7%) or to change to antacid and H<sub>2</sub>-receptor antagonists (30.3%).
- 82% of respondents who would continue PPI therapy would continue with omeprazole (as per the case scenario), usually at a daily dose of 20 mg regularly or 20 mg as required, with the time to next review ranging from one to six months.
- Respondents who recommended therapy other than PPIs suggested ranitidine (14.7%) and simethicone/magnesium/aluminium (Mylanta) (10.2%) as an antacid. When stepping down to antacids and H<sub>2</sub>-receptor antagonists was recommended, time to next review ranged from one month to six months.
- If Mr Lee remained asymptomatic at the next review, 55.2% respondents would continue the PPI therapy, 26.9% would change the dosing regimen (mostly to 'as required' dosing for the existing PPI), and 17.9% would stop the PPI (with most recommending an antacid or H<sub>2</sub>-receptor antagonist instead).

## Serious adverse events associated with PPI use

- Potential serious adverse events in patients using PPIs identified by respondents include:
  - blood dyscrasias (57.0%)
  - interstitial nephritis and impaired renal function (40.0%)
  - liver abnormalities (37.0%)
  - Stevens–Johnson syndrome (34.0%).
- Respondents suggested the following advice to alleviate Mr Lee's concern regarding potential kidney problems due to PPI use:
  - reassuring the patient that it is a rare adverse event (54.0%)
  - recommending renal function monitoring if using a PPI long term or if the patient becomes unwell (41.0%) and
  - explaining to the patient that PPIs are metabolised in the liver and can therefore be used safely in renal diseases (30.0%).

## **Managing lifestyle issues**

- Practical advice given by respondents on lifestyle changes included:
  - Encouraging smoking cessation by recommending bupropion or varenicline (48.0%), nicotine replacement therapy (28.0%) or contacting Quitline (24.0%).
  - walking 30 minutes a day 5 days a week (48.0%), seeing a dietitian (26.0%) and improving quality of food intake (17.0%) to manage weight
  - limiting alcohol intake to standard levels (54.7%), planning alcohol-free days, consuming low-alcohol drinks (35.8%) and visiting alcohol rehabilitation services (18.9%) to manage alcohol intake
  - engaging family/friend support (55.3%), realising the financial and cardiovascular benefits of lifestyle changes (26.8%) and getting involved in lifestyle management programs (21.4%).

# Results in detail

## Continuing PPI therapy

When asked if they would recommend continuing PPI therapy for Mr Lee, 67% of respondents indicated they would continue using it, while 33% would not. Table 1 summarises the main reasons for their recommendations.

Table 1: Reasons for continuing or discontinuing PPI therapy	
Reasons for continuing PPI therapy	% of respondents* (n = 67)
Symptom-driven therapy	38.8
Recurrence of symptoms	37.3
Lifestyle issues contributing to symptoms	17.9
Step down to lower dose and as required dosage	17.9
Effective therapy for Mr Lee	16.4
No observable adverse effects with low-dose therapy for long-term	7.5
Reduces risk of oesophageal cancer	4.5
Other reasons <sup>†</sup>	3.0
Reasons for discontinuing PPI therapy	% of respondents* (n = 33)
Symptom free for last 5.5 months with normal endoscopy	72.7
Chose to step down to antacids or H <sub>2</sub> -receptor antagonists	30.3
Addressing existing lifestyle issues would relieve the symptoms	15.1
Possibility of adverse events	15.1
Chances of recurrence of symptoms	12.1

\* Respondents may have more than one response

† Includes investigating for *Helicobacter pylori* infection and because antihypertensive medicines may cause reflux

Respondents were asked to specify the medication (if any) they would recommend for Mr Lee (PPI or other medication), including the dose and the time to next review (Tables 2–4).

Table 2: Recommended therapy	
Respondents who recommended continuing PPI therapy	% of respondents* (n = 67)
<b>Proton pump inhibitors</b>	
Omeprazole (as already used in the case scenario)	82.0
Esomeprazole	7.5
Pantoprazole	6.0
Rabeprazole	4.5
<b>H<sub>2</sub>-receptor antagonists</b>	
Ranitidine	3.0
<b>Antacids</b>	
Simethicone/magnesium/aluminium (Mylanta)	1.5
Respondents who recommended discontinuing PPI therapy	% of respondents* (n = 33)
H <sub>2</sub> -receptor antagonists (Mainly ranitidine and famotidine)	39.4
No drug therapy recommended	36.4
Antacids (Mainly simethicone/magnesium/aluminium (Mylanta) and alginic acid/aluminium/sodium bicarbonate (Gaviscon))	36.3

\* Respondents may have more than one response

<b>Table 3: Dosage of recommended medication</b>		
<b>Medication/dosage</b>	<b>Median time to next review (months)</b>	<b>% of respondents</b>
<b>Omeprazole</b>		<b>(n = 55)</b>
20 mg as required	3	38.3
20 mg regularly (as already used in the case scenario)	6	32.7
10 mg regularly	2	12.7
10 mg as required	3	12.7
Dosage not stated	4.5	3.6
<b>Esomeprazole</b>		<b>(n = 5)</b>
20 mg as required	2	60.0
40 mg regularly	1	40.0
<b>Pantoprazole</b>		<b>(n = 4)</b>
40 mg regularly	3	75.0
20 mg as required	6	25.0
<b>Rabeprazole</b>		<b>(n = 3)</b>
20 mg as required	4.5	67.0
10 mg regularly	2	33.0
<b>Ranitidine</b>		<b>(n = 13)</b>
150–300 mg as required	3	53.8
150–300 mg regularly	6	46.2
<b>Antacids</b>		<b>(n = 11)</b>
Simethicone/magnesium/aluminium (Mylanta) 10–30 mL as required	2	81.8
Alginic acid/aluminium/sodium bicarbonate (Gaviscon) 15–20 mL as required	2.5	18.2

Respondents were asked if they would continue, stop or change the medication they recommended for Mr Lee if he remained asymptomatic at the next review. More than half (56.8%) indicated that they would continue the regimen, 27.3% would change the medication or regimen, and 15.9% would stop the medication. Table 4 summarises the reasons.

<b>Table 4: Suggested treatment options after review</b>	
<b>Reasons for continuing the regimen (as specified in question 1b)</b>	<b>% of respondents* (n = 50)</b>
For symptom relief	38.0
Possibility of recurrence of symptoms	30.0
Recommended medication (as specified in question 1b) is successful in preventing symptom recurrence	20.0
Safe and costs less to patient	12.0
Presence of lifestyle issues contributing to symptoms	10.0
Other (Investigate again and use antacid/ H <sub>2</sub> -receptor antagonist)	8.0
No response	12.0

*(Continued next page)*

Table 4: Suggested treatment options after review (continued)	
Reasons for changing the regimen	% of respondents* (n = 24)
To step down (includes discontinuing PPI and 'as required' therapy)	33.3
Recommended medication (as specified in question 1b) is successful	29.2
Possibility of recurrence of symptoms	16.7
Alternative medication is safe and costs less	12.5
Use H <sub>2</sub> -receptor antagonists and antacids for symptom management	12.5
Use lifestyle management to prevent symptom recurrence	8.3
Reasons for stopping the regimen	% of respondents (n = 14)
Patient is asymptomatic after taking the recommended medication (as specified in question 1b)	50.0
Use lifestyle management to prevent symptom recurrence	21.4
Trial of medication cessation is appropriate	14.4
Use H <sub>2</sub> -receptor antagonists and antacid for symptom management	7.1
No response	7.1

\* Respondents may have more than one response

The recommended changes to the regimen (as in question 1b) are described in Table 5.

Table 5: Recommended changes to PPI therapy after review	
Changes to PPI therapy (as in question 1b) after review	% of respondents (n = 18)
Change from regular PPI dosing to 'as required' dosing	61.3
Try lower dose of the current PPI	16.6
Change from PPI to H <sub>2</sub> -receptor antagonist/antacid	11.1
Try higher dose of the current PPI	5.5
Change from 'as required' dosing to regular use	5.5



## Practice points

- Reserve endoscopy for patients with suspected complications, atypical or alarm symptoms, or poor response to acid suppression.<sup>1,2</sup>
- Prescribe a standard-dose of PPI once daily for 4–8 weeks.<sup>2</sup> Initial therapy heals oesophagitis in more than 70% of patients.<sup>3</sup> Restart previously successful therapy in patients who return with relapse.<sup>2</sup>
- Tell patients to take PPI medication 30 minutes before meals.<sup>2</sup> All PPIs have comparable clinical efficacy in symptom control.<sup>4</sup> Refer patients for endoscopy if response is inadequate after 8 weeks.<sup>2</sup> Inadequate adherence or dosing is the main reason for lack of response to PPI therapy.<sup>5</sup>
- Consider cessation of PPI therapy if the patient is asymptomatic after initial therapy. Around 20% to 40% of patients do not require further PPI therapy for up to 1 year after successful treatment of GORD.<sup>3</sup>
- *H. pylori* associated ulcer disease and GORD often coexist.<sup>1</sup> Consider testing and treating for *H. pylori* infection in patients who require long-term PPI therapy.<sup>6</sup>
- Consider either continuous low-dose or symptom-driven low-dose therapy if maintenance PPI is required.<sup>2,3</sup> In clinical trials of six months to 1 year, 55% of patients remain symptom free with

continuous low-dose therapy.<sup>7</sup> Symptom relief and satisfaction with low-dose symptom-driven therapy was similar to that of continuous low-dose therapy in patients with mild to moderate GORD symptoms.<sup>8</sup> These strategies are also cost-effective and preferred by patients.<sup>9</sup>

- Judicious use of PPIs for GORD can potentially save costs and reduce the risk of adverse events.

## Serious adverse events associated with PPI use

Respondents were asked to list potential rare but serious adverse events in patients using PPIs (Table 6).

Table 6: Potential serious adverse events due to PPI therapy	
'Potentially serious' adverse events indentified	% of respondents* (n = 100)
<b>Haematological</b>	
Blood dyscrasias (includes agranulocytosis, thrombocytopenia)	57.0
<b>Gastrointestinal</b>	
Liver abnormalities (includes hepatitis, abnormal liver function tests, jaundice)	37.0
Gastric abnormalities (includes hyperplasia, polyps, atrophy, gastritis)	19.0
Other abnormalities (includes colitis, carcinoma and pancreatitis)	15.0
<i>Clostridium difficile</i> infection	12.0
<b>Renal</b>	
Interstitial nephritis and impaired renal function	40.0
<b>Dermatological</b>	
Stevens–Johnson syndrome	34.0
Other (includes skin reactions and alopecia)	11.0
<b>Musculoskeletal</b>	
Osteoporotic fractures	11.0
Muscle weakness and arthralgia	8.0
<b>Endocrine</b>	
Hepatic encephalopathy	15.0
Others (includes impotence, gyanecomastia and hyponatremia)	5.0
<b>Others</b>	
Hypersensitivity reactions/anaphylaxis	18.0
Cardiac complications and drug interactions	6.0
<b>Respiratory</b>	
Community acquired pneumonia	3.0

\* Respondents may have more than one response

- Only 17.9% of participants mentioned acute interstitial nephritis and *C. difficile* infections as serious adverse events.



### Practice points

- Consider the possibility of rare but serious adverse effects when prescribing PPIs. To minimise risk, prescribe PPIs for the shortest possible time and at the lowest effective dose. Review the need for ongoing therapy regularly, particularly in the elderly, patients with multiple comorbidities and those taking multiple medications.<sup>10</sup>

- PPI use is associated with an increased risk of hospital- and community-acquired *C. difficile* infection.<sup>11,12</sup> All currently available PPIs are implicated in causing acute interstitial nephritis.<sup>10,13</sup>
- Evidence from large case–control studies suggests an increased risk of community-acquired pneumonia with PPI use.<sup>14–16</sup>
- Case–control studies report a modest, but significant association between PPI therapy and hip fracture.<sup>17</sup> Risk increased with duration of therapy and when patients took high doses of PPI for more than 1 year.<sup>18</sup>
- The risks of gastric and colorectal cancer due to PPI use are not observed in any studies and therefore seem to be theoretical risks only.<sup>10</sup> Do not monitor cobalamin levels routinely in patients who are on continuous PPI with adequate diet.<sup>19</sup>
- Other rare adverse events due to PPI use are gyanecomastia, myalgia, myopathy, arthralgia, raised liver enzyme levels, hepatitis, jaundice, thrombocytopenia, leucopenia, skin reactions (including Stevens–Johnson syndrome, toxic epidermal necrolysis, photosensitivity) and hypersensitivity reactions.<sup>20</sup>

Respondents were asked to respond to Mr Lee’s concern about possible serious kidney problems while using a PPI (Table 7).

<b>Table 7</b>	
<b>Response to patient’s concerns</b>	<b>% of respondents* (n = 100)</b>
Reassure the patient that serious kidney problems are rare adverse events	54.0
Monitor renal function — for long-term use and if patient becomes unwell	41.0
Explain that PPI is a safe medicine, as it is metabolised in liver and can be used in renal disease	30.0
Explain to the patient that his father’s condition (diabetic nephropathy) is not related	16.0
Discuss risks and benefits of treatment	13.0
Check baseline renal function	12.0
Explain that making lifestyle changes will reduce risk due to PPI use	9.0
Explain that using H <sub>2</sub> -receptor antagonists/antacid will reduce risk due to PPI use	4.0
Explain that patients older than 75 are at high-risk	2.0



### **Practice points**

- PPI-induced nephritis is a rare idiosyncratic reaction to either the medication or its metabolite and is difficult to predict.<sup>13</sup> In a 10-year study in Australian teaching hospitals 18 of 28 cases of acute interstitial nephritis were associated with PPI use.<sup>21</sup>
- The symptoms of PPI-induced nephritis are non-specific and include weight loss, fatigue, malaise, nausea and vomiting.<sup>13,22</sup>
- PPI-induced nephritis has a good prognosis and physicians should monitor for signs and symptoms in first week following therapy. If suspicious, assess renal functioning (serum creatinine and urine analysis), withdraw PPI and refer to a nephrologist if confirmed. Prescribing PPIs for the shortest possible time and only when indicated could further prevent the risk.

## Managing lifestyle issues

Respondents were asked to list practical advice that they would give to patients who find it difficult to adhere to routine lifestyle advice on smoking, weight reduction and alcohol consumption. Table 8 summarises the advice.

<b>Table 8: Advice to patient to manage lifestyle issues</b>	
<b>Smoking cessation</b>	<b>% of respondents* (n = 100)</b>
Discuss using bupropion or varenicline	48.0
Discuss using nicotine-replacement therapy	28.0
Call and discuss with Quitline	24.0
Get family support/counselling or consider seeing a psychologist	15.0
Ration cigarettes and avoid triggers	9.0
Try hypnotherapy	5.0
Reducing smoking will reduce the cardiovascular risks and costs	4.0
<b>Weight reduction</b>	<b>% of respondents* (n = 100)</b>
Exercise regularly — walk 30 minutes a day, 5 days a week	48.0
See a dietitian	26.0
Improve quality of food (low-fat and GI diet, reduce portion size and snacks between meal)	17.0
See an exercise physiologist or join support groups	16.0
Join weight-loss programs such as <i>Weight Watchers</i> , do yoga/Pilates or join a gym	6.0
Try food diary and monitor food intake	3.0
Educate that weight reduction reduces cardiovascular risks	2.0
<b>Reduce alcohol consumption</b>	<b>% of respondents (n = 53)</b>
Limit alcohol intake to standard levels	54.7
Consume low-alcohol drinks and plan alcohol-free days	35.8
Refer to alcohol rehabilitation unit / Alcoholics Anonymous group / family and friend support	18.9
Understand risks of hazardous intake	11.3
Consider use of acamprosate	5.7
<b>General advice</b>	<b>% of respondents* (n = 56)</b>
Engage family and friend support or consider cognitive therapy	55.3
Discuss the financial and cardiovascular benefits of a healthier lifestyle	26.8
Join lifestyle-management programs or acupuncture/meditation treatment	21.4
Reinforce importance of regular visits / weekly review	16.1
Educate the mechanism of aggravating factors and risks	14.3
Identify reasons and limit activities that encourage smoking/drinking	10.7
Educate that symptoms of gastro-oesophageal reflux disease would improve with the lifestyle measures	7.1

\* Respondents may have more than one response



## Practice points

- In clinical trials impact of lifestyle changes in the management of GORD are not adequately evaluated.<sup>1</sup> Obesity, smoking, alcohol and fatty foods are risk factors for GORD.<sup>23</sup>
- Advise lifestyle changes for patients with, or at high risk for, GORD (see Box 1). Improper dietary habits and absence of regular exercise are also important risk factors for developing non-communicable diseases.<sup>24</sup>

### Box 1: Lifestyle and dietary modifications in management of GORD<sup>1,2,25</sup>

#### Lifestyle modifications

- Engage in moderate exercise such as jogging for at least 30 minutes a day
- Reduce weight to keep BMI < 25 kg/m<sup>2</sup>
- Avoid recumbent position for 3 hours after meals
- Elevate the head of the bed when sleeping

#### Dietary modifications

- Avoid eating large and/or high-fat meals in the 3 hours before bedtime
- Avoid eating too fast
- Avoid drinking specific beverages such as alcohol, caffeinated drinks and carbonated drinks
- Avoid eating specific foods such as high-fat foods, spicy foods, chocolate and citrus food

- Cognitive behaviour therapy, relapse prevention and motivational interviewing are the mainstay of management of alcohol dependence.<sup>26</sup> Use acamprosate and naltrexone as an adjunct to psychosocial interventions. These drugs are modestly effective in reducing relapse, delaying return to drinking and reducing the number of drinking days.<sup>27</sup>
- Identify smokers using the 5A approach, as recommended by RACGP (Box 2).

### Box 2: The 5A framework<sup>28</sup>

- **Ask** about and document tobacco use at every opportunity
- **Assess** motivation and confidence to quit — 'Are you interested in quitting?'
- **Advise** the smoker to stop
- **Assist** the smoker to stop
- **Arrange** follow-up to maintain non-smoking

- Recommend use of pharmacotherapy (nicotine-replacement therapy, varenicline and bupropion) to increase chance of cessation and as an aid to quitting.<sup>28</sup>

# Commentary 1

## Key points

- PPI treatment is highly effective for acid-related symptoms; however, recurrence of symptoms is common after stopping therapy, usually because of ongoing disease processes and risk factors.
- All PPIs work well, and long-term treatment is generally very safe, with life-threatening events being rare. Increased risks are documented for interstitial nephritis, osteoporosis, hip fracture and infectious complications (pneumonia and gastrointestinal infections); however, the absolute risks are small and should be minimised by appropriate dosing.
- When long-term medication is required, this should be titrated down to the lowest dose consistent with adequate control of symptoms.
- Stepping down or conversion to on-demand therapies are both acceptable options.
- PPIs are most effective if given before a meal that is expected to induce symptoms.

## The case scenario

Mr Lee reported burning upper abdominal pain that responded initially to omeprazole, suggesting an acid-related aetiology. His symptoms relapsed on withdrawal of the omeprazole and responded to reinstitution of therapy, confirming the acid-sensitive nature of the symptoms.

He does not have alarm symptoms, and has had an upper-gastrointestinal endoscopy, which is appropriate given his age and other risk factors (for gastric cancer especially). Although he does not describe heartburn (retrosternal burning feeling that rises) the most likely diagnosis is non-erosive reflux disease (NERD). Peptic ulcer disease is possible, but it would be unusual to present for the first time in a 60-year-old man with no new risk factors, such as having recently started an NSAID.

We are not told Mr Lee's *Helicobacter pylori* status, which would be of greatest relevance if he had been shown to have had peptic ulcer disease.<sup>29</sup> *H. pylori* is not associated with GORD (it seems to be negatively associated on an epidemiological level). In any case, unless we believe that his symptoms are due to an undiagnosed peptic ulcer, eradication of *H. pylori* is unlikely to cure them, as chronic *H. pylori* gastritis is asymptomatic in most cases. We can be reasonably sure therefore that:

- he does not have serious underlying upper gastrointestinal pathology to explain his symptoms, which are most likely due to NERD
- unless the underlying cause can be addressed, he will require some form of ongoing acid suppression to adequately control his symptoms.

## Lifestyle issues

There is little evidence for significant benefit from encouraging lifestyle changes in the management of dyspepsia. Mr Lee is a smoker and this may be contributing to his upper-gastrointestinal symptoms, but clearly there are many other factors operating and there is no evidence that smoking cessation would improve his epigastric burning.

He is overweight and, while obesity is associated with GORD (most strongly in women); there is again little formal evidence that losing weight improves symptoms of reflux. Once again he has other strong reasons for losing weight and, although his symptoms are part of the overall picture, it would be unrealistic to promise that weight loss would result in symptomatic improvement. Unless he has nocturnal symptoms, elevating the head of the bed or avoiding late night food is unlikely to provide significant benefit.

If Mr Lee can identify specific foods that are associated with symptoms, he can avoid those

foods or (see later) undertake strategies to reduce the subsequent symptoms. Typically the foods that are expected to cause symptoms are fatty and spicy foods, but some patients report symptoms after eating quite bland foods (e.g. cereals or bread — even in the absence of coeliac disease). It is important not to impose unnecessary food restrictions and Mr Lee should be sure that there is a clear relationship between a particular food and symptoms before limiting it in his diet.

### **Ongoing acid suppression**

As discussed above, it is most likely that Mr Lee will require some degree of ongoing acid suppression, and it will be good practice to determine the lowest dose of medication consistent with good control of his symptoms. So far we know that his symptoms are adequately controlled on 20 mg of omeprazole, but that he has significant symptoms when off acid suppression (sufficient to cause him to re-present 2 weeks after stopping therapy).

There is no reason to change him to an alternative PPI, as the current one is effective and has not caused problems. The initial trial of cessation of therapy was reasonable, as it is known that about one-third of patients with endoscopy-negative reflux disease will not relapse for some time after PPI withdrawal. However, with a trial off therapy having failed, it is unlikely that a second trial of cessation will be effective.

Options for reducing therapy from this point are to either step down through doses (and possibly medications), or to move directly to a prn regimen (effectively stopping therapy, but with a backup). Mr Lee is not on a high dose of omeprazole, so step down could be started by changing to 10 mg daily, 20 mg second-daily or possibly daily therapy with an H<sub>2</sub>-receptor antagonist. If he remains well he could then be stepped down further or switched to prn medication. If he develops recurrent symptoms, he should move back up to the level of acid suppression that gave him adequate control of his symptoms.

Moving directly to prn therapy, he could use omeprazole (10 or 20mg), an H<sub>2</sub>-receptor antagonist or even intermittent antacid therapy, depending on his wishes and the severity and frequency of his previous symptoms. When

using prn PPI therapy, it is important to remember that the onset of action of PPIs can take an hour or two and that prn therapy with antacids or H<sub>2</sub>-receptor antagonists may provide more rapid symptomatic control (although a shorter duration of action). If using prn PPI it is often advantageous for patients to take the medication before the meal that is expected to cause the symptoms. The reason for this is that PPIs have a relatively short half-life in plasma and only affect active acid pumps, so it is most effective to have the PPI 'on board' at the time that digestion begins rather than playing 'catch up' when symptoms have appeared after the meal.

### **PPI use and adverse effects**

Mr Lee is concerned about the potential toxicity of PPIs and, while this is a valid concern, it needs to be seen in perspective and the alternatives to therapy must be evaluated.<sup>30</sup>

Interstitial nephritis is a recognised (although relatively uncommon) adverse effect of PPI therapy, and may not be fully reversible. At present there are no guidelines or evidence suggesting that routine monitoring of renal function is required or cost-effective in patients starting a PPI. Interstitial nephritis is idiosyncratic, and it is unlikely that Mr Lee's father's renal problems are relevant to this issue.

Diarrhoea and headache are other adverse effects occasionally seen when a PPI is started and may respond to a change in medication (presumably due to differences in PPI metabolism). In any event, if a patient has not had acute problems, concerns about toxicity relate largely to long-term risks.

As a class of drugs, PPIs have had an extraordinarily good track record of safety.<sup>31</sup> At the time of introduction there were significant concerns about the possible induction of neuroendocrine tumours, and subsequently potential acceleration of gastric atrophy or carcinoma or colorectal cancer (via hypergastrinaemia). None of these has been borne out in practice despite widespread use over a significant period of time; however, current guidelines recommend that, to slow the rate of gastric atrophy, patients on long-term regular treatment with a PPI have *H. pylori* eradicated if present.<sup>32</sup>

Epidemiological studies have demonstrated increased risks of osteoporosis, hip fracture, pneumonia — both community and hospital acquired — and gastrointestinal infections, with *C. difficile* infection in elderly hospitalised patients of greatest concern.<sup>30,33</sup> There are also reported links with vitamin B12 deficiency.

The relative risks of the bone and pulmonary problems are small; however, the large numbers of patients using PPIs mean that these may translate into significant numbers at a population level. There is no evidence linking PPIs to blood dyscrasias, liver toxicity or Stevens–Johnson syndrome. There is emerging evidence that PPIs may reduce the effect of clopidogrel; however, whether this is a class effect or specific to one or more drugs is yet to be fully defined.

In conclusion, as with all drugs, the risks of therapy need to be balanced against the benefits and the alternatives examined. Mr Lee can be reassured that the absolute risks to his health from the medication are small and will be reduced further by using the minimum level of medication consistent with control of his symptoms, and that the level of risk from his prescribed medication of course pales into insignificance when compared with that related to his cigarette consumption.

His alternatives will be to continue to experience dyspeptic symptoms or to consider other therapies for his NERD (fundoplication would be both unwarranted and more risky than continuing PPI).

# Commentary 2

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The rationale for drug use in gastro-oesophageal reflux disease (GORD) is to relieve the patient's symptoms, heal any oesophagitis and reduce the risk of complications.<sup>20</sup> Before making remarks on the responses that have been received, some comments on the scenario are required.

## The case scenario

One year ago Mr Lee presented with symptoms consistent with (GORD) and was prescribed omeprazole 20 mg daily, which was discontinued 6 months later. Discontinuation was appropriate because Mr Lee was asymptomatic, but the doctor should have reviewed Mr Lee earlier. PPI therapy should be reviewed 4–8 weeks after initial therapy at the standard-dose for GORD.<sup>2,20</sup>

Patients with predominant daytime symptoms should take the PPI 30 minutes before breakfast; those with nocturnal symptoms 30 minutes before the evening meal.<sup>2</sup> Earlier review is important to identify those who have not responded to treatment who should undergo endoscopy to rule out more serious pathology.<sup>2</sup>

Mr Lee's symptoms returned within 2 weeks of discontinuing the omeprazole, and an endoscopy was performed. As most of you are no doubt aware, a normal endoscopy does not rule out GORD, as more than half of patients with GORD have no endoscopic abnormality.<sup>1</sup>

However, it would have been good to have known whether Mr Lee was tested for *H. pylori*. Although this organism does not appear to be important in GORD or its complications, it is a cause for dyspepsia that sometimes can be confused with GORD. If Mr Lee was to continue his PPI use it would be important to know that he is *H. pylori* negative because continuing use of PPI in the presence of *H. pylori* may lead to atrophic gastritis and eventually gastric cancer.<sup>2,6,20</sup> However, it was also important to note that, apart from the endoscopy being normal, Mr Lee had no alarm symptoms.

When Mr Lee was reviewed the second time after being restarted on the omeprazole 20 mg daily for another 6 months, it would have been particularly interesting to ask him about his regularity of use (adherence). If he had missed doses and had developed symptoms, this would have helped considerably in being able to answer the first question.

On the information given in relation to Mr Lee, it would seem that there are two options. One option would be to step-down to omeprazole 10 mg. The other alternative is to continue the omeprazole 20 mg but on a prn basis (particularly if Mr Lee has never tried using it this way before to see how frequently he required it). Intermittent use of PPIs reduces costs and does not appear to increase risks from GORD.

There is no reason for changing Mr Lee's PPI, as all PPIs are similarly effective, Mr Lee is not taking other medications that interact with the omeprazole, and it appears to be working without any side effects.

Making lifestyle changes that may improve Mr Lee's risk of GORD are always important but cannot be guaranteed to work. Therefore a step-down approach to the minimum PPI dose (and frequency) for symptom control is appropriate.<sup>2</sup> If Mr Lee rarely used his PPI at the lowest dose, he could try using H<sub>2</sub>-receptor antagonists or antacids (but these also have adverse effects and interact with other medications).

## Review of therapy

There was a range of responses as to how soon Mr Lee should be reviewed. Review between 1 and 2 months would be a sufficient time to know whether a further step-down would be possible. This would be consistent with current guidelines.<sup>2,20</sup> Unfortunately patients do not always return as requested, so it is always important to discuss PPI usage whenever a patient returns for a repeat script and is using these medications.

If Mr Lee remained asymptomatic at the next review after the regimen initiated above, a further step-down in his PPI would be appropriate; that is, if placed on 10 mg daily, step-down to 10 mg prn (or if on 20 mg prn, step-down to 10 mg prn). If Mr Lee had not required his PPI at all, over-the-counter H<sub>2</sub>-receptor antagonists or antacids (for future recurrence of symptoms) or no medication at all are options for him. However, in practice I find that most of my patients require a PPI at least on a prn basis.

### **PPI and adverse effects**

From the responses received it would appear that the message about the rare but serious risk of *C. difficile* infection<sup>11,34,35</sup> is not well known within the medical community. A larger proportion (40%) were aware of the rare but serious risk of PPI-induced interstitial nephritis.<sup>21,36</sup> This PPI complication can be induced soon after initiation or up to a year later and can be asymptomatic. Other rare but serious risks of PPI use, such as blood dyscrasias and hepatic damage, were mentioned more commonly by respondents.

In responding to Mr Lee's concerns about his personal risk of renal disease (because of his father's nephropathy), it may be useful to know more about his father's illness(es) and the role of genetic versus lifestyle factors. Pharmacogenetics is evolving and, if PPIs contributed to his father's renal disease, it is best to not use them.

However, the scenario states that Mr Lee's father has diabetic nephropathy (no other causes). Therefore, one needs to explain that the risk is very low and that the risks from his other activities such as smoking and any excess alcohol use pose a much higher risk of causing serious problems like heart disease, liver disease, stroke and cancer.

It should also be explained that there are other options for his GORD, such as H<sub>2</sub>-receptor antagonists or antacids or even taking nothing at all. For all these options explain the benefits and risks of each so that Mr Lee is well informed to make his own decision about what he would like to do.

Adherence is more likely if there is 'buy-in' from the patient.

### **Lifestyle factors**

Most patients have lifestyle factors that are important contributors to their medical problems. However, it is often difficult for patients to make healthy lifestyle changes. It would be important to know what methods they have used to change and what success they have had.

Using medications that can help overcome addiction (e.g. to smoking) can be useful but need to be combined with advice on strategies that can help patients achieve their goals (that fit in with their lifestyle). Seeking the support of family and friends is important.

Advising increased exercise is good but again needs to be discussed in more detail to enable the patient to build it into their daily lifestyle (with clear achievable goals). Regular review is also important to both congratulate on successes and to discuss failures and thus, hopefully, new ways to progress. Seeing a dietitian could be enhanced by having the patient complete a diary (food, drink and exercise). Some patients find their own solutions once they can see what they are doing from their diary.

Alcohol abuse is one of the most difficult problems to treat. A patient may gain control (via medication, rehab programs and counselling) for a period of time only to regress whenever a new stress arrives. It is still worthwhile trying the range of methods, as there are a few long-term successes (and most of these achieve control only by abstaining totally from alcohol).

In conclusion, from my experience most patients with GORD require lifelong treatment with either intermittent or regular PPI, H<sub>2</sub>-receptor antagonist or antacid. Lifestyle changes can be achieved and, although often not as successful in overcoming GORD, undoubtedly have far-reaching benefits on the patient's overall health.

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