Is your patient’s proton pump inhibitor still needed?

Proton pump inhibitors (PPIs) are among the most common medicines used in Australia.¹ They are highly effective and when used in accordance with evidence-based guidelines are considered safe.² When used for longer than recommended at high doses they are associated with adverse effects, especially in older patients.³⁻⁷

Older people make up the largest proportion of DVA patients dispensed PPI therapy; in 2013 PPIs were dispensed to over 70,000 DVA patients whose average age was 87 years.⁸

Many older people have a high prevalence of comorbidities which often means they take multiple medicines.⁹ ¹⁰

In addition to these comorbidities, DVA patients often have a number of health and wellbeing issues specific to them which increases the complexity of their care needs.¹¹ Unnecessary medicine use further contributes to poor health outcomes and reduced quality of life.¹⁰, ¹²

An Australian study of 41,000 DVA patients initiated on a PPI for gastro-oesophageal reflux disease (GORD) found:

- Two-thirds did not have their initial dose reduced or therapy stopped after eight weeks of treatment.
- A third continued the initial dose for one year.¹³
- The average duration of PPI treatment without reducing the dose was almost 20 weeks, much longer than the recommended 4-8 weeks.¹³⁻¹⁵

### Key points

- **When starting a PPI for GORD** explain that the expected duration of treatment is four to eight weeks
- **Review the need for ongoing use** in all your patients receiving a PPI longer than eight weeks
- **Trial stepping down the dose and stopping therapy in patients with GORD whose symptoms are well controlled and taking a PPI for longer than eight weeks**
Review the need for ongoing PPI use

☐ Ask: Is a PPI still needed after eight weeks of treatment for GORD?

Patients with two or more episodes of gastro-oesophageal reflux symptoms per week or whose symptoms are severe enough to significantly impair quality of life are considered to have GORD.\(^1\) These patients often require a daily PPI at a standard dose for four to eight weeks before stepping down the dose and stopping (see Table 1).\(^1\), \(^4\), \(^6\)

Up to 30% of patients remain asymptomatic after stopping a PPI.\(^1\) GORD has a natural history of chronicity and relapse. Hence, a large proportion of patients have symptoms that recur from time to time and fluctuate in severity.\(^9\)

Some patients might need intermittent therapy to control recurring symptoms.\(^9\)

☐ Ask: Is the initial indication for PPI use still present?

If you do not know why your patient is using a PPI, check if they have had an endoscopy, hospitalisation for a bleeding ulcer, ongoing NSAID use, or have a history of heartburn or dyspepsia to help determine if stepping down the dose or stopping is appropriate.\(^1\), \(^7\) If the indication remains unknown, try stepping down to the lowest effective dose or stopping the PPI.\(^1\), \(^8\)


Consider a Home Medicines Review (HMR) or a Residential Medication Management Review (RMMR). To find out more about the benefits of an HMR and the HMR process, refer to Not sure of the HMR process at: www.veteransmates.net.au/documents/10184/38810/Nov_2016_GP_Insert.pdf

A minority of patients might require ongoing PPI use including those with:\(^17\) to \(^20\)

- Barrett’s oesophagus
- severe oesophagitis
- a history of GI bleeding or those at high risk of a GI bleed who have not had a previous bleed
- long-term NSAID use in those at risk of NSAID-induced peptic or gastric ulceration
- Zollinger-Ellison syndrome
- oesophageal scleroderma
- oesophageal stricture.

In this select group of patients consider referring to a gastroenterologist for consultation, if you are considering trialling a reduction in dose or require advice about ongoing PPI use.

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**Step-down the dose or stop the PPI**

**Table 1: Oral proton pump inhibitor dosages for GORD\(^9\), \(^14\), \(^17\)**

<table>
<thead>
<tr>
<th>Proton pump inhibitor</th>
<th>Standard dose for four to eight weeks</th>
<th>Low dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>esomeprazole</td>
<td>20 mg once per day*</td>
<td>step-down to a low dose</td>
</tr>
<tr>
<td></td>
<td>10 mg sachets once per day or 10 mg omeprazole once per day</td>
<td></td>
</tr>
<tr>
<td>lansoprazole</td>
<td>30 mg once per day</td>
<td>step-down to a low dose</td>
</tr>
<tr>
<td></td>
<td>15 mg once per day</td>
<td></td>
</tr>
<tr>
<td>omeprazole</td>
<td>20 mg once per day</td>
<td>step-down to a low dose</td>
</tr>
<tr>
<td></td>
<td>10 mg once per day</td>
<td></td>
</tr>
<tr>
<td>pantoprazole</td>
<td>40 mg once per day</td>
<td>step-down to a low dose</td>
</tr>
<tr>
<td></td>
<td>20 mg once per day</td>
<td></td>
</tr>
<tr>
<td>rabeprazole</td>
<td>20 mg once per day</td>
<td>step-down to a low dose</td>
</tr>
<tr>
<td></td>
<td>10 mg once per day</td>
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</tbody>
</table>

*Only consider a high dose e.g. 40 mg once per day for a further four weeks if the response to the initial dose of 20 mg per day is inadequate.\(^9\) If your patient is taking 40 mg once a day, step-down the dose before stopping.

☐ Trial stepping down to the lowest effective dose and stopping the PPI

- If your patient has uncomplicated GORD and symptoms are well controlled after a maximum of eight weeks,\(^1\), \(^4\), \(^6\) A previous Veterans’ MATES topic targeting PPI use found that over half of respondents did not realise they could reduce their PPI dose.\(^21\)

☐ If symptoms are not well controlled after eight weeks, confirm optimal PPI use

- confirm compliance,\(^14\)
- review medicines that might be:
  - causing or worsening symptoms including NSAIDs, bisphosphonates, tetracyclines, nitrates or calcium
channel blockers and change or cease where appropriate.\textsuperscript{9}  

- impairing the effect of the PPI including rifampicin or enzalutamide and increase the dose of the PPI accordingly.\textsuperscript{3}  
- If compliance is satisfactory, consider:  
  - endoscopy if the diagnosis is unclear, your patient complains of difficulty or pain when swallowing, or complications are suspected.\textsuperscript{14} If no other cause is evident, consider continuing the same PPI at the previous dose,\textsuperscript{16} or at a high dose for a further four to eight weeks.\textsuperscript{5, 14}  

A standard dose given twice a day is more effective than a double dose given once a day. Then step-down to the lowest effective dose and stop. If symptoms persist, consider other diagnoses, for example functional dyspepsia,\textsuperscript{16} peptic ulcer\textsuperscript{9} or testing for \textit{Helicobacter pylori}.\textsuperscript{17}  
- referral for specialist advice if symptoms persist and diagnosis still remains unclear.\textsuperscript{9}  

\section*{Why stepping down the dose is most effective}

\begin{itemize}
  \item Stopping a PPI abruptly can result in rebound symptoms in some patients.\textsuperscript{14} If you are stopping the PPI abruptly, consider a regular or ‘as needed’ H\textsubscript{2}-receptor antagonist or an antacid until symptoms are controlled.\textsuperscript{14}  
  \item Stepping down the dose appears to be the most effective way to avoid rebound symptoms.\textsuperscript{14, 22} Individualise the dose and taper slowly before stopping. Advise your patients to return for review if their symptoms recur and their quality of life is reduced.\textsuperscript{14}  
  \item As a general guide, step-down the dose by half each time or give a dose on alternate days.\textsuperscript{14}  
  \item If symptoms are not adequately controlled on the step-down dose, recommence the lowest effective dose and frequency of PPI until symptoms are controlled.\textsuperscript{14, 16} If symptoms are unmanageable, consider referral to a gastroenterologist for expert advice.\textsuperscript{14}  
  \item Explain to your patients that their symptoms might vary from time to time because of changes in their diet, weight, smoking or stress levels and that they might need to take a PPI on days when symptoms occur.\textsuperscript{14}  
  \item Evidence suggests oesophageal sensitivity or an altered perception in the oesophagus plays a significant role in generating reflux symptoms in some patients. Stress, anxiety and reduced quality of life is thought to play a part in increasing the perception of reflux symptoms in some patients with no obvious features of the disease.23, 24  
\end{itemize}

Managing anxiety-related conditions might be helpful in reducing reflux symptoms in these patients. DVA can pay for treatment for any mental health condition without the need for the condition to be accepted as related to service. This is known as non-liability health care. For further information contact DVA on 133 254 or 1800 555 254 or visit: www.dva.gov.au/nlhcc

\section*{Follow-up after stopping PPI use}

Ask your patient to make an appointment four weeks after stopping their PPI.\textsuperscript{17} At that appointment keep encouraging your patient to:  

\checkmark Adhere to diet and lifestyle modifications that are effective

Highlight to your patient that losing weight if they are overweight and stopping smoking if they smoke can help to reduce symptoms.\textsuperscript{25} Evidence to support reduction of weight or waist circumference, especially in obese people, and smoking cessation is significant.25-27  

Dietician, physiotherapy and exercise physiology services are available to eligible DVA patients which might help support patients to make these changes. For further information visit: www.dva.gov.au/providers/allied-health-professionals  

Eligible DVA patients have access to medicines for nicotine dependence. Encourage contact with the national smoking Quitline on 13 7848 or at: www.quitnow.gov.au  

Raising the head of the bed can help reduce symptoms if they are worse at night or disturb sleep.26 Adjustable bed heads and bed blocks can be provided to eligible DVA patients through the “Rehabilitation Appliances Program (RAP) National Schedule of Equipment” at: www.dva.gov.au/sites/default/files/files/providers/rehabilitation/rap_schedule.pdf  

Evidence for the effectiveness of other lifestyle and dietary modifications is limited.\textsuperscript{3} Advise your patients to continue dietary changes only if they are effective, to avoid unnecessary food restrictions.\textsuperscript{14}
Kidney disease
A large prospective cohort study found for every 25 patients treated with a PPI, there would be 1 extra case of chronic kidney disease than if they were not treated.30 Twice daily dosing appeared to be associated with a higher risk compared to once daily dosing.30 A large population-based study of more than 290,000 participants found for every 187 older patients treated with a PPI, there would be 1 extra case of acute kidney injury including interstitial nephritis, than if they were not treated.3

Clostridium difficile infection
A meta-analysis of studies found for every 67 patients treated with a PPI, there would be 1 extra case of Clostridium difficile infection than if they were not treated. For every 121 patients treated with a H₂-receptor antagonist, there would be 1 extra case of Clostridium difficile infection.31 Gut microbiota and gastric acidity play key roles in maintaining healthy and balanced immune and inflammatory processes.32, 33 Overuse of PPIs can lead to a significant shift in gastric and intestinal microbial composition and stomach pH, which is thought to predispose patients to debilitating infections, including Clostridium difficile-associated diarrhoea, Salmonella and Campylobacter infections.31, 32, 34-36

Vitamin B₁₂ deficiency
Several studies suggest there is an association between PPI use and an increased risk of vitamin B₁₂ deficiency.37 Older patients are already at an increased risk of vitamin B₁₂ deficiency due to impaired absorption, and use of other prescribed medicines, e.g. metformin.37

Pneumonia
Several studies suggest an association between PPI use and pneumonia exists.5, 7, 28 A large study of DVA patients aged 65 years and over found for every 80 patients treated with a PPI, there would be 1 extra patient hospitalised for pneumonia than if they were not treated with a PPI.7

Hypomagnesaemia
In 2011, the Therapeutic Goods Administration warned of a potential association between prolonged PPI use and hypomagnesaemia-related adverse events including tetany, seizures, delirium and cardiac arrhythmias.39 While it was reported these events occurred rarely, there was no reliable way to predict which patients might be at risk but that some medicines, including loop and thiazide diuretics, might cause or worsen hypomagnesaemia.39

Other new research
There does not appear to be any association between long-term PPI use and the development of gastric cancer.19, 40 A systematic review of patients using PPIs for longer than three years found an increased prevalence of gastric hyperplasia and raised gastrin levels. Helicobacter pylori-positive patients had a higher risk of developing hyperplasia compared with Helicobacter pylori-negative patients, but no cancers were found in any of the studies explored.40

Footnote: A Hong Kong study showed long-term PPI use was associated with an increased risk of gastric cancer in Helicobacter pylori-positive patients who had received eradication therapy. Patients taking a daily PPI for three or more years were at the highest risk. It is important to note that the Helicobacter pylori species found in Hong Kong are more virulent when compared to those usually found in Australia and to date this finding has not been shown in an Australian patient cohort.41

Full reference list available on the website: www.veteransmates.net.au
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References

21. Australian Government Department of Veterans’ Affairs Health Claims Database, University of South Australia, OUMPRC. [Accessed April 2018].