Deprescribing proton pump inhibitors

CPD

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Background
Proton pump inhibitors (PPIs) are indicated for disorders including peptic ulcer disease and gastro-oesophageal reflux disease; however, they are often used for longer and at higher doses than recommended, or for indications that are not supported by evidence.

Objective
The aim of this article is to outline evidence-based approaches to deprescribing PPIs.

Discussion
PPIs are generally well tolerated; however, use beyond eight weeks is rarely indicated and increases the risk of adverse events. PPI deprescribing should be considered when there is no indication for long-term therapy. Evidence supports a patient-centred approach to PPI deprescribing involving stepping down the dose before ceasing or switching to pro re nata (PRN; 'as needed') use. Abrupt PPI discontinuation may result in short-term rebound acid hypersecretion that can mimic symptom return. This can be minimised with gradual dose tapering prior to discontinuation and managed with PRN treatment. Prescribers should discuss the rationale for PPI deprescribing and involve patients in developing the deprescribing plan.

THE INTRODUCTION OF PROTON PUMP INHIBITORS (PPIs) in the 1990s revolutionised the treatment of acid-related conditions such as peptic ulcer disease (PUD) and gastro-oesophageal reflux disease (GORD). PPIs rapidly resolve symptoms by irreversibly binding to the proton pump in the parietal cell, inhibiting gastric acid secretion and increasing stomach pH.[1] More than 15 million PPI prescriptions were dispensed through the Australian Pharmaceutical Benefits Scheme in 2020–21.[2]

The Gastroenterological Society of Australia and The Royal Australian College of General Practitioners recommend regular review of long-term PPI use with the goal of dose reduction and cessation.[3,4] PPIs are often used beyond the 4–8-week duration recommended for most indications. An international review reported PPIs were overused or improperly used by 11–84% of patients.[5] Recent reports suggest that 22–63% of PPIs are continued longer than is likely necessary (ie continued despite no indication for long-term therapy).[6,7] Fifteen per cent of Australian adults receive at least one PPI prescription each year, suggesting a large number of Australians are exposed to the risk of adverse events without additional benefit.[6]

PPI indications

For most PPI indications, short-term treatment is recommended (Box 1). The Australian *Therapeutic guidelines* recommend PPIs be trialled for GORD and dyspepsia if antacids, diet and lifestyle modifications fail to resolve symptoms. This trial involves prescribing a PPI once daily, to be taken 30 minutes before a meal, for a period of 4–8 weeks to allow the mucosa time to heal.[8] If symptoms persist after 8 weeks, it is recommended to check adherence and dosing, before reassessing the need for continued treatment. Other short-term indications include *Helicobacter pylori* eradication and treatment of aspirin or nonsteroidal anti-inflammatory drug (NSAID)-related gastric and duodenal ulcers in low-risk patients. PPIs provide effective first-line treatment options for GORD and dyspepsia; however, patients should be referred for gastroscopy if they are experiencing alarm symptoms such as anaemia, dysphagia, odynophagia, haematemesis, melaena, vomiting or weight loss, particularly in older adults.[8]

Long-term PPI therapy (ie beyond eight weeks) is indicated for Barrett's oesophagus, Zollinger–Ellison syndrome and patients with severe erosive disease (Los Angeles grade C/D), peptic stricture or a history of bleeding gastric ulcers (Box 1).[8,9] Similarly, long-term PPI therapy is indicated for gastroprotection among patients with a high bleeding risk taking NSAIDs or aspirin.[1,10,11] When patients have a clear and current indication for long-term therapy, then the benefits

are likely to outweigh any risk of harm. These patients are not candidates for deprescribing. However, recent American Gastroenterological Association guidelines state that apart from patients with Zollinger–Ellison syndrome, there is a dearth of evidence to support the use of double-dose PPIs when compared with maintenance-dose PPIs.[11]

Adverse events associated with PPI use

Potential adverse events from short-term PPI use include headache, nausea, vomiting, diarrhoea, abdominal pain, constipation and flatulence.[12] Observational studies report short-term PPI use is associated with an increase in the risk of acute interstitial nephritis.[13] Observational studies also report long-term PPI therapy has been associated with a small increased risk of enteric bacterial infections (eg *Clostridium difficile* infections, odds ratio [OR]: 1.74; 95% confidence interval [CI]: 1.47, 2.85), fractures (OR: 1.33; 95% CI: 1.15, 1.54), community acquired pneumonia (hazard ratio [HR]: 1.82; 95% CI: 1.27, 2.54) and reduced levels of magnesium (OR: 1.43; 95% CI: 1.08, 1.88) and vitamin B12 (HR: 1.83; 95% CI: 1.36, 2.46).[14–17] However, it is not possible to directly infer causation from these studies.[17,18] A large randomised controlled trial examined adverse events associated with PPI when compared with placebo use over three years. An increased risk of enteric infections was observed among PPI users (absolute risk = 0.4%); however, no other differences in adverse events were observed between groups.[19] While this was a large study, it may have been underpowered for detecting rare adverse events. Patients with newly diagnosed vitamin B12 deficiency, enteric infections or fractures should have their condition investigated, including a review of the necessity of their long-term PPI treatment. Supplements including vitamin B12, calcium or vitamin D should be initiated in accordance with evidence-based guidelines regardless of PPI use. Although there is uncertainty about causality of some associations, long-term PPI therapy without a clear indication unnecessarily increases the risk that patients are exposed to adverse events.[9,11]

Box 1. Recommendations for long-term (>8 weeks) and short-term (≤8 weeks) proton pump inhibitor treatment[11]

Long-term use (>8 weeks)

- Barrett's oesophagus
- Zollinger–Ellison syndrome
- Clinically significant severe erosive oesophagitis (LA grade C/D)
- Peptic strictures
- Oesophageal scleroderma
- Eosinophilic oesophagitis
- Gastroprotection from NSAIDs or aspirin in patients at high risk of GI bleed*
- Prevention of pulmonary fibrosis progression

Short-term indications (≤8 weeks)

- *Helicobacter pylori* eradication
- Treatment of aspirin or NSAID-related gastric and duodenal ulcers in patients at low risk
- GORD
- Dyspepsia

**AGA guidelines consider patients to be high risk if age >60 years, severe medical comorbidity, using multiple NSAIDs or aspirin, taking and antithrombotic or oral corticosteroid.*

AGA, American Gastroenterological Association; GI, gastrointestinal; GORD, gastro-oesophageal reflux disease; LA, Los Angeles classification of gastro-oesophageal reflux disease; NSAID, nonsteroidal anti-inflammatory drug

What is the best approach to deprescribing PPIs?

Two different deprescribing approaches have shown success in clinical trials:[9]

- gradual dose tapering to the lowest available dose for a defined period of time prior to discontinuation (eg 4–8 weeks or shorter depending on patient preference; refer to Box 2 for PPI dosing and dosages available in Australia)
- PPI discontinuation and switching to pro re nata (PRN; 'as needed') treatment.

A third approach is discontinuing the PPI and switching to an H2 antagonist. This may be trialled if it aligns with patient preferences; however, the likelihood of symptoms returning has been shown to be greater following a switch to a H2 antagonist when compared with dose tapering or switching to PRN treatment.[9,20]

Some healthcare providers find it practical to commence gradual dose tapering prior to discontinuation followed by switching to PRN treatment. This stepped approach combined with non-pharmacological interventions may allay patient fears of symptom return and gain the patient's trust in the deprescribing process. Non-pharmacological interventions include changes in lifestyle factors such as diet, weight and avoiding stress.

Box 2. Proton pump inhibitor (PPI) availability

Initial therapy, high-dose PPIs:

- Esomeprazole 20 mg, 40 mg
- Lansoprazole 30 mg
- Omeprazole 20 mg
- Pantoprazole 40 mg
- Rabeprazole 20 mg

Maintenance therapy, low-dose PPIs:

- Lansoprazole 15 mg
- Omeprazole 10 mg
- Pantoprazole 20 mg
- Rabeprazole 10 mg

Will symptoms return when PPIs are deprescribed?

Patients and prescribers may fear that symptoms will return when PPIs are discontinued.[21] Approximately 80% of patients with GORD remain symptom free after gradual dose tapering or discontination.[22,23] However, abrupt cessation can precipitate rebound acid hypersecretion in 10–50% of patients, which can be mistaken for a return of upper gastrointestinal symptoms, even in healthy adults without gastrointestinal disorders.[24–26] The clinical significance of rebound acid hypersecretion remains unclear,[9,27] and while rebound acid hypersecretion is not necessarily a failure of PPI deprescribing, it can be concerning for patients.

Gradual dose tapering and switching to PRN use have been shown to be appropriate and effective

ways of managing rebound acid hypersecretion.[20,28] Alternate-day low-dose PPI use before discontinuation has been shown to be more effective than abrupt cessation for managing rebound acid hypersecretion.[29] It is important to discuss the possibility of symptom return with patients. Patients should be reassured that rebound acid hypersecretion may only last a few days and can often be adequately managed with PRN PPIs or non-prescription antacids or H2 antagonists.

How to discuss PPI deprescribing with patients

When initiating a PPI, it is prudent to provide information about the intended treatment duration and follow-up. However, patients who have been using PPI for the long term may not have been provided with or recall information about intended duration. Engaging patients and carers in shared decision making increases deprescribing success.[30–32]

After confirming the patient's symptoms have resolved, it is important to explain that the gastrointestinal mucosa is likely to have healed, and they are a good candidate for deprescribing. This can then be followed by a discussion of deprescribing options (eg gradual dose tapering prior to discontinuation then PRN use) to determine which approach is most suitable. This conversation may require identifying and allaying any fears about deprescribing. The possibility of rebound acid hypersecretion and preferences for a strategy to mitigate it should be discussed.[21]

A useful phrase to gain patient acceptance is to talk about 'a trial of deprescribing', reassuring patients that the PPI can be restarted again if symptoms reoccur. It is important to create a personalised deprescribing plan and identify monitoring and support the patient may need. This may involve documenting what patients should do if their symptoms come back. If re-prescribing is required, it is beneficial to annotate on the prescription the duration of use before review is required and provide a limited number of repeats.

Several resources are available to facilitate shared decision making about PPI deprescribing (Box 3). Providing patients with an educational booklet outlining the benefits and harms of PPIs may increase patient–prescriber discussions about deprescribing.[30] Similarly, a patient decision aid used during a patient–healthcare provider consultation has been shown to increase patients' knowledge and generate realistic expectations regarding deprescribing outcomes.[31] Additionally, information about the decision to trial deprescribing and the outcome should be communicated with other relevant healthcare professionals and documented in medical and prescription records where possible.

Conclusion

The decision to continue or deprescribe a PPI should be patient centred and based on the evidence of benefit or harms. The majority of patients receiving PPIs can trial deprescribing once their symptoms have resolved. Gradual dose tapering prior to discontinuation followed by PRN treatment can help avoid or manage potential rebound acid hypersecretion.

Key points

- Deprescribing is not recommended in patients with Barrett's oesophagus, Zollinger–Ellison syndrome, severe erosive disease, peptic stricture or history of bleeding gastric ulcers, or when PPIs are used for gastroprotection in patients at high risk of bleeding taking NSAIDs or aspirin.
- PPI deprescribing should be considered when there is no clear indication for long-term therapy.
- Patients should be involved in developing the deprescribing plan.
- Gradual dose tapering prior to discontinuation followed by PRN treatment can help avoid or manage potential rebound acid hypersecretion.

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Box 3. Resources to support proton pump inhibitor (PPI) deprescribing

Patient resources

- Patient educational brochures, www.deprescribingnetwork.ca/s/Stomach-pills-for-acid-reflux_PPIs.pdf
- Patient decision aid, https://deprescribing.org/resources/deprescribing-patient-decision-aids
- PPI deprescribing pamphlet, https://deprescribing.org/wp-content/uploads/2018/08/Deprescribing-Pamphlet_PPI_ENG_CFP.pdf
- NPS MedicineWise PPI patient action plan, www.nps.org.au/assets/50240b737233cd47-a615f8d13d0c-NPS1993_SSDSM_PAP_v5.1.pdf

Healthcare provider resources

- Canadian deprescribing algorithm and guideline, https://deprescribing.org/resources/deprescribing-guidelines-algorithms
- NPS MedicineWise – Reviewing proton pump inhibitors (PPIs) for gastro-oesophageal reflux disease (GORD), www.nps.org.au/assets/NPS2357_Reviewing_PPIs_Algorithm_v3_FINAL.pdf
- NPS MedicineWise – Managing GORD with PPIs in primary care, www.nps.org.au/professionals/managing-gord-with-ppis-in-primary-care#insights
- Four-minute whiteboard video on PPI deprescribing for general practitioners, www.deprescribingnetwork.ca/deprescribing-ppis
- Tasmanian deprescribing guide, www.primaryhealthtas.com.au/wp-content/uploads/2018/09/A-Guide-to-Deprescribing-Proton-Pump-Inhibitors-2019.pdf
- Choosing Wisely Canada toolkit (Bye Bye PPI), https://choosingwiselycanada.org/toolkit/bye-bye-ppi

GORD, gastro-oesophageal reflux disease

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