A GUIDE TO

deprescribing

# PROTON PUMP INHIBITORS

## KEY POINTS

- **Short term use of PPIs for acid-mediated gastrointestinal conditions is effective and safe.**
- **PPIs are very widely used so adverse effects that occur less frequently may still be observed in normal clinical practice.**
- **Many people with GORD do not experience a relapse after cessation of PPIs.**
- **Consider stopping PPIs after an initial course of 4-8 weeks of treatment and symptom resolution.**
- **If PPIs continue to be required, use of the lowest dose or of intermittent treatment may be effective.**
- **If PPIs are ceased, ongoing monitoring for recurrence of symptoms is appropriate.**
- **The best way to avoid problems when stopping PPIs is to ensure they are only initiated where indicated, and that they are used for the shortest possible time.**

## CONTEXT

**This guide considers the use of proton pump inhibitors in the management of gastrointestinal disorders.**

## RECOMMENDED DEPRESCRIBING STRATEGY

Many people are taking PPIs without a clear indication for their use.

Determining a history of gastrointestinal bleeding, endoscopy, non-steroidal anti-inflammatory drugs (NSAID) use and previous symptoms may assist with determining whether deprescribing is appropriate.

Consider stopping PPIs after an initial course of 4-8 weeks of treatment and symptom resolution.

If an initial attempt to reduce the dose or cease the PPI are unsuccessful, further attempts may be made after 2-4 weeks of continued therapy.

If PPIs are ceased, ongoing monitoring for recurrence of symptoms is appropriate.

An algorithm for the deprescribing of PPIs is shown below:

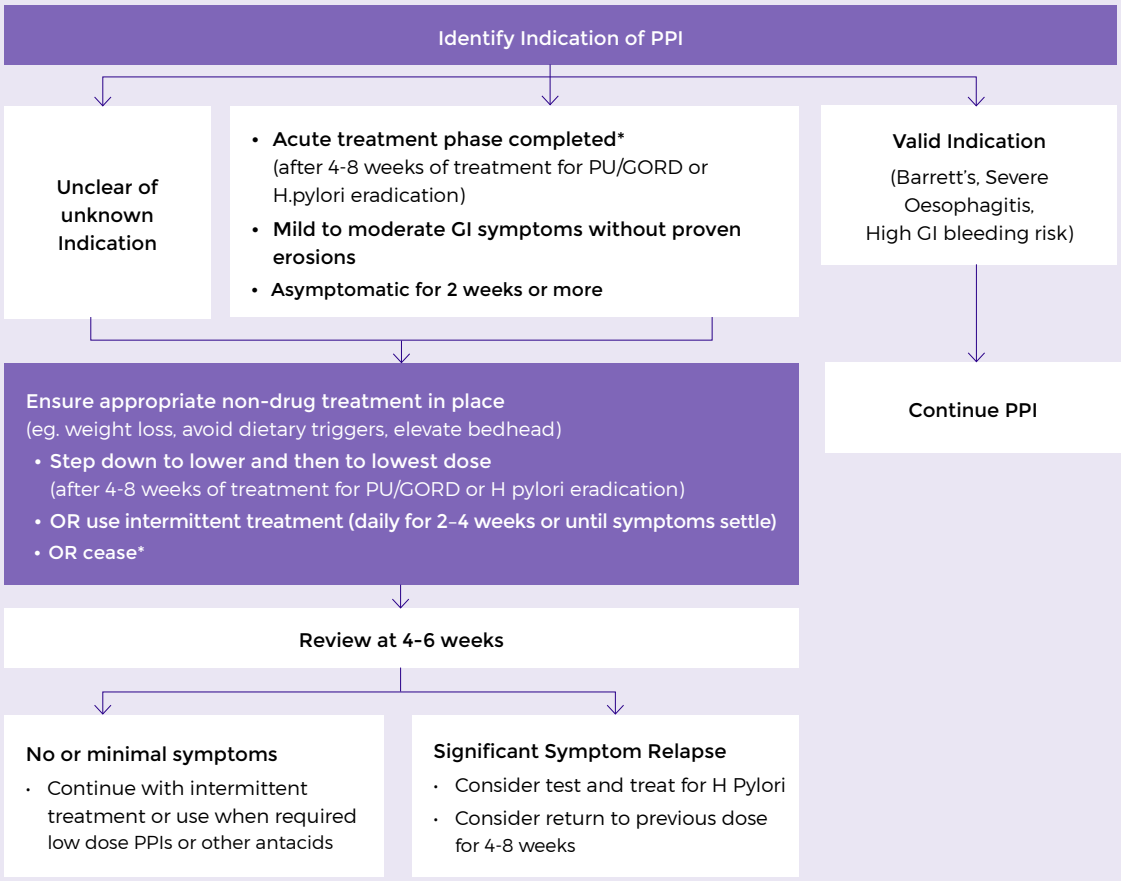
## EFFICACY

PPIs are amongst the most commonly used agents in Australia with over 20.5M prescriptions in 2014.[1] They are effective and generally safe for the symptomatic management of acid-mediated gastrointestinal disorders. PPIs are however increasingly being used for long periods and often without a proper indication for their use.[2]

PPIs are effective at relieving upper gastrointestinal symptoms of gastro-oesophageal reflux disorders (GORD) and healing oesophagitis.[3] Approximately 85% of patients with erosive oesophagitis have complete healing at 8 weeks (70% in the first 4 weeks).[4] Only around 30% of patients with GORD have erosive disease and the efficacy of PPIs in patients without erosions (i.e. with non –erosive gastritis) is lower than that in those with established erosions. A systematic review of remission and symptom relief in patients with non-erosive oesophagitis reported a net remission rate of 29% for PPIs.[5] In terms of symptom relief alone, lower doses of PPIs have been shown to be as effective as the full doses that are recommended for healing.[6]

GORD is most often a recurring condition, with only a minority of patients requiring continuous therapy. After an initial course of treatment (4-8 weeks) for GORD, reducing the dose to a minimum, changing to intermittent use (2-4 weeks of treatment at a time) or ceasing the agent is often possible.

## DEPRESCRIBING ALGORITHM




In a limited number of patients, maintenance therapy may be required for ongoing symptom control, however many patients are appropriately managed with as required treatment. Recommended treatment, maintenance and step down doses are shown in **Table 1** below.

| DRUG | TREATMENT DOSE (4-8 WEEKS) | MAINTENANCE DOSE (IF SYMPTOMS PERSIST) | STEP-DOWN DOSE |
|---|---|---|---|
| **Esomeprazole** | 40mg once daily | 20mg once daily | 10mg sachets available |
| **Lansoprazole** | 30mg once daily | 30mg once daily | 15mg once daily |
| **Omeprazole** | 20mg once daily | 20mg once daily | 10mg once daily |
| **Pantoprazole** | 40mg once daily | 40mg once daily | 20mg once daily |
| **Rabeprazole** | 20mg once daily | 20mg once daily | 10mg once daily |

Table 1: Treatment and Maintenance doses of PPIs

A few hypersecretory conditions may require long term treatment with PPIs, sometimes at a higher dose. These include:

- Symptom management and prevention of complications in patients with gastro-oesophageal reflux disease who have frequent, significant symptoms that are not controlled by lower or intermittent doses of PPIs.[3]
- Symptom management in patients with severe oesophagitis, oesophageal stricture and/or oesophageal scleroderma.
- Healing and prevention of relapse in patients with H pylori associated disease where eradication therapy has failed or is contraindicated.
- Prophylaxis in patients with long-term NSAIDs who are at high risk of NSAID- induced ulceration.[7]
- Healing and/or prevention of ulcers in patients with Zollinger-Ellison syndrome.

A number of differing discontinuation regimens (including abrupt discontinuation) were used in six studies reviewed by Haastrup et al.[26] Discontinuation without deteriorating symptom control was reported across all six studies ranging from 14% to 64%, with discontinuation persisting for more than a year. Two of the studies included dose reduction as an endpoint and showed that 30–50% of the patients were able to lower the dose.[26]

## ADVERSE EFFECTS

PPIs are very widely used (over 20M prescriptions in 2014 in Australia) in a broad range of patient populations and only infrequently cause adverse effects. As a result of their common use, the occurrence of PPI related problems, particularly in more susceptible patient groups, may be significant.

Less serious adverse effects of PPIs reported in clinical trials include diarrhoea (1-4% of patients), headache (1-2%) and nausea (~1%). The frequency of these adverse effects is comparable to that reported for placebo in these trials.

A number of less common, but significantly more serious, adverse effects have been linked to the long-term (and some to short term) use of PPIs.[8,9,10] These studies are all observational, population based reviews and the associations with PPIs may not be causative.

| DUE TO REDUCED OR MODIFIED ABSORPTION OF NUTRIENTS |
|---|
| vitamin B12 deficiency[11] |
| reduced calcium absorption with increased bone loss and increased fractures |
| decreased magnesium absorption |
| reduced iron absorption |
| **DUE TO ALTERED PH OF THE GASTRIC CONTENTS** |
| increased enteric infections (including *Clostridium difficile*) |
| increased risk of community and hospital acquired pneumonia |
| increased development of fundic gland polyps |
| **DUE TO SPECIFIC CHEMICAL CHARACTERISTICS OF THE PPI MOLECULE (IDIOSYNCRATIC)** |
| acute interstitial nephritis and possibly other kidney disease |
| interference with bio-availability or metabolism of other medications |
| thrombocytopaenia (case reports only) |
| rhabdomyolysis (case reports only) |

Table 2: Mechanisms and Examples of possible PPI Adverse Effects

### KIDNEY DISEASE

The long term use of PPIs has been associated with the development of both acute and chronic kidney injury.

Hospitalisation from acute kidney injury was evident in 13.49 per 1000 in over 66 year old people in Ontario (median age 74 years old) who were users of PPIs compared to 5.46 per 1000 person years in matched controls (Absolute Risk Increase 8.03 per 1000 person years; NNH 125).[12]

When they examined admissions later confirmed as due to acute interstitial nephritis the rate for PPI users was 0.32 per 1000 person years compared to 0.22 per 1000 person years in controls (ARI 0.21 per 1000 person years; NNH 476). They did not find any difference in the risk of acute kidney injury amongst the four PPIs being taken. Hazard ratios were 2.56 for lansoprazole, 2.94 for omeprazole, 2.43 for pantoprazole and 2.45 for rabeprazole[12] Acute kidney injury was also examined in relation to PPI use by Lazarus et al.[13] They found that over an average of 13.9 years the absolute increase in risk of AKI in PPI users was 13.12% compared to the non-user rate of 8.61% (ARI 4.51%, NNH 22 over 13.9 years).

Lazarus et al also reported that the risk of chronic kidney disease (CKD) occurred 50% more often in PPI users compared to non-users in their retrospective study of over 10,000 participants in the Atherosclerosis Risk in Communities study. The retrospectively examined (over an average of 13.9 years) the rate of incident CKD and found a frequency of 17.39% in PPI users compared to 13.71% in non-users (ARI 3.67%; NNH 27 over 13.9years). They found that twice daily dosing with PPIs was associated with a higher risk of CKD (1.46 fold) compared to once daily dosing (1.15 fold) and the researchers also observed that there was no association between risk of CKD and H2 receptor antagonist use.[13]

### HYPOMAGNESAEMIA

A systematic review and meta-analysis found that PPIs were linked to the development of hypomagnesaemia.[14] They found a pooled relative risk of hypomagnesaemia was 1.43 (95% CI 1.08-1.88), with a higher rate in concurrent diuretic users than non-users. The higher risk of hypomagnesaemia in patients taking both PPIs and diuretics was confirmed in a small prospective study by Richardson.[15]

### CLOSTRIDIUM DIFFICILE

Changes in acid content of the gastrointestinal tract may alter bacterial growth. The association between PPI use and Clostridium difficile (C. difficile) associated diarrhoea has been reviewed.[16,17] Both papers identified an increased relative risk of approximately 40%, although absolute risk was not quantified. Both authors also identified that the risk of C difficile infection was not present with H2 receptor antagonists and was increased to over two fold for patients concurrently taking broad spectrum antibiotics.

Recurrence of Clostridium difficile infection occurs 50% more often in patients who continue PPIs after an initial C difficile infection.[18] Other factors that combined with continuous PPI use to further increase the risk of recurrence were:

- Age older than 75 years
- Extended length of hospital stay
- Concurrent use of antibiotics

### PNEUMONIA

The reduced acid content of the stomach induced by PPIs is thought to contribute to bacterial overgrowth and an increase in risk of pneumonia. Two meta-analyses showed a 34-39% increase in frequency of community acquired pneumonia in PPI users compared to non-users.[19,20]

The majority of patients in the observational studies reviewed in these meta-analyses had GORD, which can in itself, increase the risk of pneumonia. Filion et al collated information on patients using PPIs who were taking them as gastro-protection (against GI bleeding from NSAIDs) and did not have diagnosed GORD.[21] They were not able to find an association between PPI use and hospitalisation for community-acquired pneumonia.

### FRACTURE RISK

PPI-induced reduced absorption of calcium may result in reduced bone mineral density and an increase in fracture risk. Long term use of PPIs has been associated with reduced calcium levels and hyperparathyroidism.[22]

An updated meta-analysis of 18 studies found that PPI use could increase the risk of hip fractures (relative risk 1.26) compared to no use of PPIs.[23] The fracture risk for spinal and other site fractures was also increased 1.58 fold and 1.33 fold respectively.

Of interest, they found that both short term (less than one year) and long term (more than one year) use of PPIs had a similar increased risk, raising the possibility of a mechanism other than the impact on calcium absorption.[23]

## DISCONTINUATION SYNDROMES

### REBOUND HYPERSECRETION OF GASTRIC ACID

Rebound acid hypersecretion (an increase of gastric acid secretion above pre-treatment levels) may occur after cessation of PPIs. It is proposed that proton pump inhibition induces hypergastrinaemia and growth of histamine releasing enterochromaffin-like cells which lead to increased acid secretion once the PPI is ceased.[24]

It seems, however, that this effect is most often seen in asymptomatic volunteers, rather than people with GORD. In a systematic review of two studies on volunteers and three studies of people with reflux disease, the authors found no evidence of symptomatic rebound hypersecretion in the people with GORD.[25]

A number of differing discontinuation regimens (including abrupt discontinuation) were used in six studies reviewed by Haastrup et al.[26] Discontinuation without deteriorating symptom control was reported across all six studies ranging from 14% to 64%, with discontinuation persisting for more than a year. Two of the studies included dose reduction as an endpoint and showed that 30–50% of the people were able to lower the dose.[26]

## FACTORS TO CONSIDER

The goal of treatment with PPIs is to control symptoms at the lowest possible dose for the shortest possible duration. GORD is a relapsing/remitting condition that may be managed with intermittent use (2-6 weeks at a time) of PPIs to assist with symptom management during active phases. There are some serious acid-mediated conditions that may require long term maintenance therapy.

### IN FAVOUR OF DEPRESCRIBING

- Modification of lifestyle factors (avoiding smoking, reducing alcohol, caffeine, fat and chocolate consumption, weight loss) that independently improve GORD symptoms may allow for reduction or cessation of the PPI.
- Disappearance of GORD symptoms after an initial treatment period of 4-8 weeks with a PPI should prompt consideration of PPI cessation as many people may not relapse.
- If potentially ulcerogenic medications are ceased (e.g. aspirin, NSAIDs, corticosteroids) the ongoing use of the PPI could be reviewed..
- People with non-erosive oesophagitis or symptoms for which no specific acid-related diagnosis has been made may be more likely to benefit from intermittent rather than continuous use of PPIs.

### AGAINST DEPRESCRIBING

- People with a previous history of GI bleeding are at very high risk of subsequent bleeding. This risk is exacerbated by some medications (antiplatelets, anticoagulants, NSAIDs, corticosteroids). Such people may require long term, low dose prophylaxis.
- People with a high GI bleeding risk, who have not had a previous bleeding episode, may benefit from prophylactic use of low dose PPIs. These include people who are:
  - taking long-term non-selective non-steroidal anti-inflammatory agents
  - taking dual antiplatelet therapy
  - taking anticoagulants
- Established oesophagitis or other acid-mediated oesophageal damage (e.g. Barrett's Oesophagus) may require long-term treatment on specialist advice.
- Ongoing, uncontrolled GORD symptoms may require ongoing treatment.

## RESOURCES

- QUICK REFERENCE GUIDE
- GENERAL INFORMATION
- ALLOPURINOL
- ANTIHYPERTENSIVES
- ANTIPLATELET AGENTS
- ANTIPSYCHOTICS
- BENZODIAZEPINES
- BISPHOSPHONATES
- CHOLINESTERASE INHIBITORS
- GLAUCOMA EYE DROPS
- NSAIDS
- OPIOIDS
- PROTON PUMP INHIBITORS
- STATINS
- SULPHONYLUREAS
- VITAMIN D AND CALCIUM

## AUTHORSHIP

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