

Long-Term Use of Proton Pump Inhibitor (PPI) Medication

Proton pump inhibitors (PPIs) are some of the most commonly prescribed medications in Australia and around the world. Over the last 30 years, PPIs have improved and resolved symptoms for patients with acid-related conditions, and prevented countless operations for peptic ulcer disease complications. However, it is widely acknowledged that PPIs are overprescribed and there are emerging concerns regarding the potential long-term complications of PPIs.

THE USE OF PPI TREATMENT

There are accepted and established indications for the use of PPI medications (Table 1).

Healing and maintenance of erosive oesophagitis
Gastro-oesophageal reflux disease
Treatment of <i>H. pylori</i> infection (in combination with antibiotics)
Short-term treatment of <i>H. pylori</i> negative peptic ulcer disease
Healing of NSAID associated peptic ulcer
NSAID induced dyspepsia
Risk reduction of at-risk patients using NSAIDs, antiplatelet agents
Pathological hypersecretory conditions
Eosinophilic oesophagitis
Short-term treatment of patients with functional dyspepsia
Barrett's oesophagus

Despite these recommendations, it is estimated that approximately 50% of all PPIs taken are inappropriate due either to an unaccepted indication for use or the excess duration of treatment. A recent study of patients attending general practices in Australia¹ confirmed similar findings, with many patients (and their doctors) not attempting to reduce or cease the PPI despite no longer meeting criteria for use.

The RACGP and Choosing Wisely Australia² have highlighted the chronic use of PPI medication as one of the 10 most important issues for GPs. Chronic and inappropriate use of PPI medications results in potential interactions with other prescribed medications, unnecessary costs to the health care system and exposure to potential long-term complications of PPI use.

CONCERNS REGARDING LONG-TERM PPI USE

Long-term complications of PPIs are of increasing concern amongst patients and doctors. These concerns are based on evidence from retrospective, observational studies that have revealed associations rather than proven cause and effect results.^{3,4} The potential complications of long-term PPI use are listed in Table 2.

Enteric infection	<i>Clostridium difficile</i> infection Small intestinal bacterial overgrowth (SIBO) Campylobacter and Salmonella infection
Renal disease	Interstitial nephritis Chronic kidney disease
Osteoporotic bone fractures	
Micronutrient deficiencies	Vitamin B12 deficiency Hypomagnesaemia Hypocalcaemia
Dementia	
Pneumonia	
GI malignancies	

- ***Clostridium difficile* infection**

Enteric infections are believed to be increased due to the reduced acid environment in the stomach. *Clostridium difficile* infections (CDI) have been associated with long-term PPI use with an estimated two-fold increased risk of CDI-associated diarrhoea. Although the use of antibiotics and increased age are still the most significant risk factors for CDI, the presence of this infection should be considered in patients on long-term PPIs with ongoing diarrhoea.

[Continued overleaf >](#)

• Renal disease

Recent observational studies have highlighted an association between long-term PPI use and chronic kidney disease (CKD). An American study⁵ involved more than 100,000 male veteran patients who were long-term PPI users compared to a matched cohort using H₂ blockers. A 1.6% annual excess risk of CKD was demonstrated. Although the mechanism is unknown, the previously identified acute idiosyncratic reaction of interstitial nephritis may represent a potential aetiology.

• Osteoporotic bone fractures

A reduction in bone mineral density and subsequent risk of fracture is a common concern with long-term PPI use⁶. The postulated mechanisms include interaction with osteoclast activity, altered calcium absorption or an increased rate of falls with PPI use. Like all the other potential complications of long-term PPI use, there is no definitive proof of cause and effect. Although studies are inconsistent, based on a recent meta-analysis, there appears to be a 25-30% increased risk of hip fracture and 50% increased risk of vertebral fractures with long-term use of PPIs.^{7,8}

• Vitamin B12 deficiency

An acidic gastric environment is required for Vitamin B12 (cobalamin) absorption. It is estimated that 2.3% of patients over 50 years have vitamin B12 deficiency, and that this is increased to 3.8% with greater than two years of PPI treatment.⁹

• Dementia

In early 2016, an observational study from Germany¹⁰ suggested a link between PPI use and dementia. Subsequent studies published from the UK¹¹, USA¹² and Finland¹³ indicated that there was no association between PPI use and dementia. At this stage, the consensus is that dementia cannot be attributed to long-term PPI use, but further studies are continuing to explore this association.

MANAGEMENT OF LONG-TERM PPI USE

Aiming for the lowest possible dose and shortest duration of treatment should be the aim for PPI treatment. Assessment of the indication for the use of PPI and regular medication review is recommended. If withdrawal or dose reduction are attempted, patients need to be aware that rebound symptoms are common. The use of alternative agents such as H₂ blockers, antacids, along with PRN dosing of PPIs are appropriate management steps. Lifestyle modifications and non-medication management should also be considered. Except for regular vitamin B12 levels, there is currently no recommendation for routine monitoring for the potential long-term complications of PPI use.

TAKE HOME MESSAGES

1. PPIs remain a very effective treatment for acid related disorders. Rationalisation of PPI medications, like all other medications, is recommended to achieve the lowest possible dose required.
2. The potential complications of long-term PPIs do not necessitate cessation nor regular monitoring of complications but rather an awareness of their potential by both GPs and specialists alike.
3. Further research and studies may better delineate the long-term complications of PPI treatment.



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