A GUIDE TO

deprescribing

phn TASMANIA
An Australian Government Initiative

primary health TASMANIA

CPS Experts in Medicines
CONSULTANT PHARMACY SERVICES

PROTON PUMP INHIBITORS (PPIs)

KEY POINTS

Short term use of PPIs for acid-mediated gastrointestinal conditions is effective and safe.

In some patients with severe GI pathology or significant risk factors, long term PPI use may be warranted.

PPIs are very commonly used medications and so adverse effects that occur with a low absolute frequency may still be observed commonly in clinical practice.

Reduction/cessation of PPIs should be considered after an initial course of 4 - 8 weeks for treatment of GORD if symptoms have resolved.

Many patients with GORD do not experience a relapse after cessation of a PPI.

If a PPI continues to be required, use of a lower dose, or on-demand treatment may be sufficient.

If an initial attempt to reduce the dose or cease the PPI is unsuccessful, further attempts may be made after 4 - 8 weeks of continued therapy.

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

CONTEXT

This guide considers the use of proton pump inhibitors for the management of upper gastrointestinal disorders in adults.

BENEFIT VERSUS HARM

	Favours Continuing Medication	Favours Deprescribing Medication
Main Benefits Reduced acid-related gastrointestinal symptoms	**Increased Benefit** • Presence of hiatus hernia, Barrett's Oesophagus, severe oesophagitis • Previous bleeding peptic ulcers • Ongoing symptoms of GORD requiring treatment • Ongoing use of gastrointestinal irritant (e.g. anticoagulant, antiplatelet, NSAID)	**Decreased Benefits** • Symptoms no longer evident • Continuous use for mild oesophagitis or intermittent symptoms
Main Harms Interstitial nephritis, altered absorption of nutrients and some medications	**Reduced Harms** • Use of low dose vs standard dose	**Increased Harms** • Concurrent diuretics • Concurrent antibiotics • Twice daily vs once daily administration

RECOMMENDED DEPRESCRIBING STRATEGY

Many patients take proton pump inhibitors (PPIs) for long periods and/or at high doses, without a clear indication for their use. Determining if there is any history of peptic ulcer disease, gastrointestinal bleeding, endoscopy, use of gastro-irritant medications (including non-prescription systemic NSAIDs or low-dose aspirin) or previous symptoms may assist with determining whether deprescribing is appropriate.

An algorithm for the deprescribing of PPIs is shown on page 2.

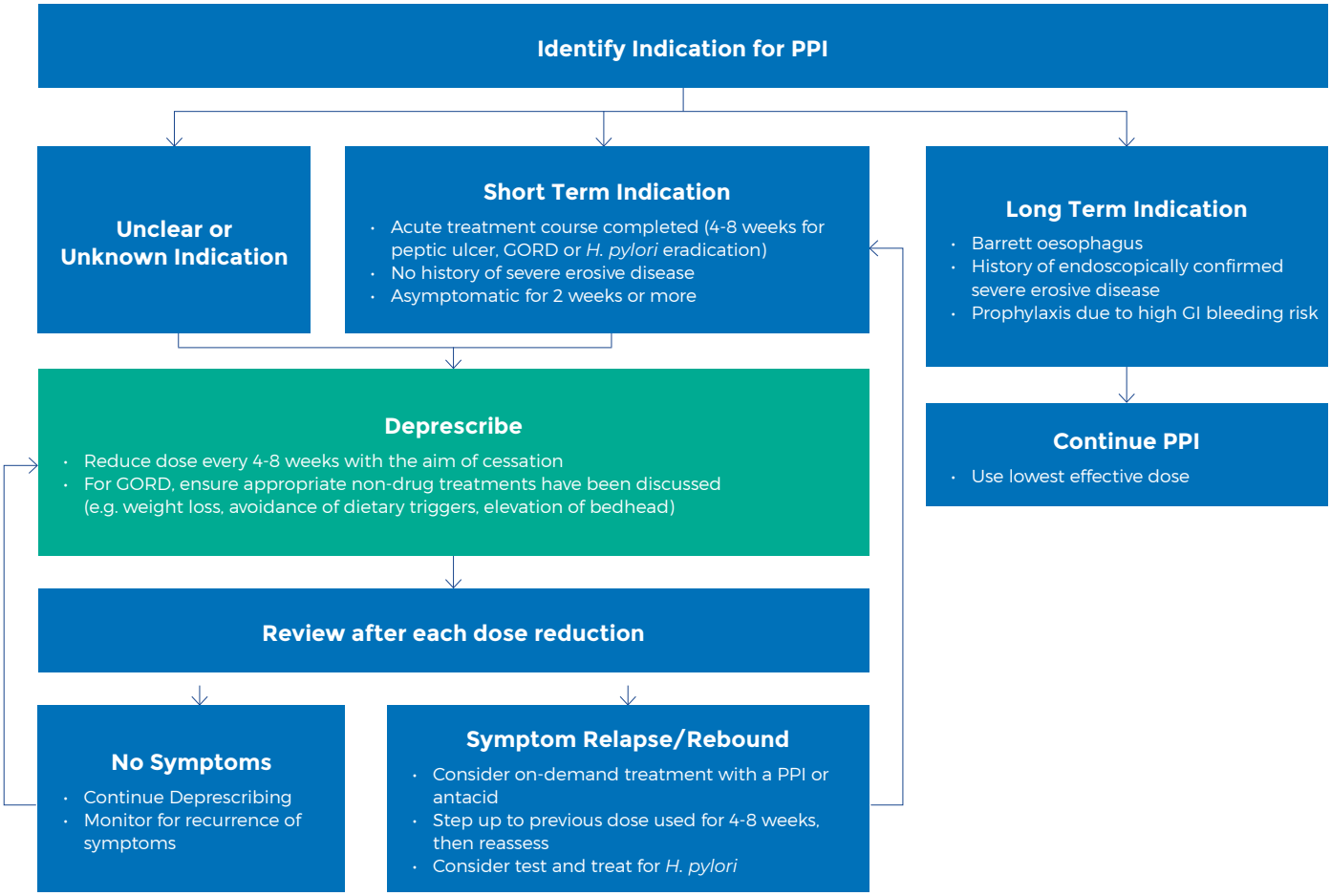

Figure 2 Algorithm for the deprescribing of PPIs

BACKGROUND

PPIs are amongst the most commonly used drugs in Australia with around 22 million prescriptions dispensed in the year to June 2021.[1] In addition, a number of PPIs are available over the counter, with direct-to-consumer advertising driving significant self-medication. PPIs are effective for the treatment of peptic ulcer disease and symptomatic management of acid-mediated gastrointestinal disorders, however, they are frequently used for long periods and/or at high doses, without a clear indication for their use.[2]

While PPIs are generally well tolerated, their use has been linked to an increased risk of fractures, pneumonia, enteric infections, vitamin and mineral deficiencies, and kidney disease, particularly among older people who make up the largest proportion of PPI users. While there is insufficient evidence to establish causation, these reports are somewhat alarming given the widespread use and often inappropriate long-term use of PPIs. This is especially relevant as PPIs when used for uncomplicated gastro-oesophageal reflux disease (GORD) can be stopped after the initial course of therapy without triggering symptom recurrence in up to 64% of people.[3] Alternatively, dose reduction, or change to on-demand dosing is often possible.

Both the Royal Australian College of General Practitioners and the Gastroenterological Society of Australia have provided recommendations on the use of proton pump inhibitors as part of the Choosing Wisely Australia initiative (see **Figure 1**).

Choosing Wisely Australia
An initiative of NPS MedicineWise

Recommendation Don't use proton pump inhibitors (PPIs) long term in patients with uncomplicated disease without regular attempts at reducing dose or ceasing.
Recommendation Do not continue prescribing long term proton pump inhibitor (PPI) medication to patients without attempting to reduce the medication down to the lowest effective dose or cease the therapy altogether.

Figure 1 Recommendations on Proton Pump Inhibitors developed for Choosing Wisely Australia.[4,5]

EFFICACY

PPIs are effective at relieving upper gastrointestinal symptoms of GORD and healing oesophagitis.[6] A systematic review of patients with non-erosive GORD reported a net remission rate of 29% due to PPI therapy.[7] In the roughly one third of patients with GORD who have erosive disease, approximately 85% prescribed a PPI experience complete healing at 8 weeks (70% in the first 4 weeks).[8]

Much has been written about differences in potency between PPIs with surrogate markers such as 'number of hours gastric pH > 4' used to compare different regimens. In clinical practice there is very little, if any, predictable difference between drugs or dosing regimens, at least in regard to symptom management of GORD. The exception to this is in erosive conditions where high dose esomeprazole (40mg daily) appears significantly more effective than standard or low intensity PPI regimens at inducing complete symptom remission (at 4 weeks) and healing of erosions (at 4 and at 8 weeks).[9]

GORD is most often a relapsing/remitting 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 on-demand dosing, or ceasing PPI therapy completely is often possible.

Standard and low intensity daily doses are shown in **Table 1**.

DRUG	STANDARD DOSE	LOW DOSE
Esomeprazole	20mg*	10mg (non-PBS)
Omeprazole	20mg	10mg
Lansoprazole	30mg	15mg
Pantoprazole	40mg	20mg
Rabeprazole	20mg	10mg

* Esomeprazole 40mg daily is available for treatment-refractory GORD or severe hypersecretory conditions.

Table 1: Standard and low doses of PPIs

A limited number of conditions may require longer term treatment with PPIs. These include:

- Symptom management and prevention of complications in patients with GORD who have frequent, significant symptoms that are not controlled by lower or on-demand doses of PPIs.[6]
- 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 taking systemic NSAIDs who are at high risk of NSAID- induced ulceration.[10]
- Prophylaxis in certain high-risk patients prescribed antithrombotic therapy
- Healing and/or prevention of ulcers in patients with Zollinger-Ellison syndrome.

The Therapeutic Guidelines recommend a standard dose PPI is used when indicated for prophylaxis in high bleed risk patients (see **Table 1**).[10] Low doses may be sufficient in some cases but it is unclear if this is consistent across all PPIs and all clinical situations.[11]

ADVERSE EFFECTS

Although PPIs only infrequently cause adverse effects, they are very widely used, and the overall occurrence of PPI related problems (particularly in more susceptible patient groups) is likely to 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.[12,13,14] See **Table 2**. Studies highlighting these issues are all observational, population-based reviews and the associations with PPIs may not be causative.

KIDNEY DISEASE

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

In a Canadian cohort study of people aged over 66 (median age 74 years old) incidence of hospitalisation from acute kidney injury (AKI) was 13.49 per 1000 person years in people who were users of PPIs compared to 5.46 per 1000 person years in matched controls (Absolute Risk Increase (ARI) of 8.03 per 1000 person years; NNH 125).[15] When researchers examined admissions for acute interstitial nephritis, the incidence in PPI users was 0.32 per 1000 person years compared to 0.11 per 1000 person years in controls (ARI 0.21 per 1000 person years; NNH 476). No difference in the risk of acute kidney injury was found between the four PPIs studied.[15]

Another study by Lazarus et al also examined incidence of AKI related to PPIs using data from over 10,000 participants in the Atherosclerosis Risk in Communities study. They found that over an average of 13.9 years, AKI occurred in 13.12% of PPI users compared to 8.61% of non-users (ARI 4.51%, NNH 22 over 13.9 years). Chronic kidney disease (CKD) also occurred more commonly in PPI users compared to non-users with a frequency of 17.39% in PPI users compared to 13.71% in non-users (ARI 3.67%; NNH 27 over 13.9 years). [16] They also 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.[16]

IRON DEFICIENCY

The role of gastric acid in dietary iron absorption has long been recognised but it is only recently that a definitive link between PPI use and iron deficiency +/- anaemia has been established. Along with a number of smaller studies, a recent population-based case-control study demonstrated an adjusted odds ratio of iron deficiency in regular PPI users compared with non-users of 3.60 (95% CI 3.32–3.91), and in intermittent PPI users of 1.51 (95% CI 1.44–1.58).[17] This effect was dose dependant, with risk greatest in patients taking high PPI doses, and time dependant, with the risk increasing with duration of therapy.

B12 DEFICIENCY

Several studies have shown a link between the use of acid suppressive therapy and the development of vitamin B12 deficiency. [18] One of the largest, a case-control study involving 24,854 cases and 178,226 controls, reported an increased risk of B12 deficiency in people who had received at least 2 years of PPI therapy (OR 1.65, 95% CI 1.58-1.73). Incidence was particularly increased in those receiving more than 1.5 PPI pills/day (OR 1.95, 1.77-2.15).[19]

HYPOMAGNESAEMIA

A systematic review and meta-analysis found that PPIs were linked to the development of hypomagnesaemia.[20] They found a pooled relative risk of hypomagnesaemia was 1.43 (95% CI 1.08-1.88), with a higher rate in those concurrently using a diuretic. The higher risk of hypomagnesaemia in patients taking both PPIs and diuretics was confirmed in a small prospective study by Begley et al.[21]

CLOSTRIDIOIDES DIFFICILE

Changes in acid content of the gastrointestinal tract may alter bacterial growth and facilitate the passage of microorganisms further into the gut. The association between PPI use and *Clostridioides difficile (C. difficile)* associated diarrhoea has been reviewed in several studies.[22,23] These studies identified an increased relative risk of approximately 40%, although absolute risk was not quantified. Concomitant use of a PPI and a broad spectrum antibiotic confered a two-fold greater risk of *C. difficile* infection than the use of a PPI alone.[23]

Recurrence of *C. difficile* infection occurs 50% more often in patients who continue PPIs after an initial *C. difficile* infection.[24] Other factors that combined with continuous PPI use to further increase the risk of recurrence were age >75 years, extended hospitalisation, and 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.[25,26] While the meta-analysis by Eom et al. did not find a significant association between PPI use and hospital acquired pneumonia (HAP)[25], one of the studies included, a prospective study by Herzig et al., demonstrated a 30% increase in risk associated with PPI use.[27]

The majority of patients in the observational studies reviewed in these meta-analyses had GORD, which can in itself, increase the risk of pneumonia. In one study looking at patients using PPIs for gastro-protection against NSAIDs, no association between PPI use and hospitalisation for community-acquired pneumonia was found.[28]

FRACTURE RISK

Long term use of PPIs has been associated with reduced calcium levels and hyperparathyroidism.[29]

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.[30] 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 impairment of calcium absorption.[30]

DUE TO REDUCED OR MODIFIED ABSORPTION OF NUTRIENTS
■ Vitamin B12 deficiency,
■ Increased fracture risk (several metabolic pathways likely involved),
■ Decreased magnesium absorption,
■ Iron deficiency
DUE TO ALTERED PH OF THE GASTRIC CONTENTS
■ Increased enteric infections (including Clostridioides 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

FACTORS TO CONSIDER

The indication for the PPI should be determined prior to consideration of deprescribing as there are several scenarios that may warrant long-term therapy. When used for dyspeptic symptom relief, the goal should be to use the lowest intensity of treatment possible for the shortest possible duration. GORD is a relapsing/remitting condition that can often be managed with short courses or on-demand PPI therapy during active phases only.

IN FAVOUR OF DEPRESCRIBING

Positive modification of lifestyle factors (stopping/reducing smoking, avoiding dietary triggers, weight loss, reducing the size of meals, raising the head of the bed) 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 or dose reduction as many patients may not relapse.

If medications that are ulcerogenic or increase the risk of GI bleeding (e.g. systemic NSAIDs, antithrombotics, oral corticosteroids), or medications which worsen GORD symptoms (e.g. nitrates, calcium channel blockers) are ceased or reduced, the need for ongoing PPI use should be reviewed.

Patients with non-erosive oesophagitis or symptoms for which no specific acid-related diagnosis has been made may be more appropriately managed with on-demand rather than continuous PPI therapy.

AGAINST DEPRESCRIBING

Patients with a previous history of GI bleeding are at high risk of subsequent bleeding. This risk is exacerbated by some medications (systemic NSAIDs, antithrombotics, oral corticosteroids) and such patients may require long term, prophylaxis with a PPI.

Patients with a high risk of GI bleeding, who have not had a previous bleeding episode, may also benefit from prophylactic use of A PPI. These include patients

- taking long term systemic NSAIDs, especially non-selective agents
- taking combinations of antithrombotic agents
- taking single antithrombotic agents if multiple significant risk factors for bleeding are present

Recurrent oesophagitis or other conditions associated with acid-mediated oesophageal damage (e.g. Barrett's Oesophagus) may require long-term PPI treatment on specialist advice.

Ongoing, severe GORD may also require long-term PPI treatment, where previous attempts at deprescribing have been unsuccessful and it is not appropriate/possible to eliminate exacerbating factors.

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.[31] The clinical relevance of this effect has been the subject of several studies that have produced mixed results. Overall, it seems likely that rebound does occur, appearing after at least 4 weeks of PPI therapy and lasting from a few days to several weeks.[32]

A number of differing discontinuation strategies (including abrupt discontinuation) were reviewed in a systematic review by Haastrup et al.[3] Discontinuation without deteriorating symptom control was reported across all six studies ranging from 14% to 64%, with discontinuation persisting for more than a year. Utilisation of a dose step down approach appeared to result in a higher rate of successful discontinuation than abrupt cessation.[3]

REFERENCES

1. PBS Expenditure and Prescriptions Report 1 July 2020 to 30 June 2021. www.pbs.gov.au/statistics/expenditure-prescriptions/2020-2021/PBS_Expenditure_and_Prescriptions_Report_1-July-2020_to_30-June-2021.pdf accessed 30th June 2022.
2. Reimer C. Safety of long-term PPI therapy. Best Pract Res Clin Gastroenterol 2013; 27: 443-454.
3. Haastrup P, Paulsen MS, Begtrup LM, Hansen JM, Jarbøl DE. Strategies for discontinuation of proton pump inhibitors: a systematic review. Fam Pract. 2014 Dec;31(6):625-30.
4. The Royal Australian College of General Practitioners: tests, treatments and procedures clinicians and consumers should question. Available at http://www.choosingwisely.org.au/recommendations/racgp accessed 30th Aug 2018.
5. Gastroenterological Society of Australia: tests, treatments and procedures clinicians and consumers should question. Available at http://www.choosingwisely.org.au/recommendations/gesa accessed 30th Aug 2018.
6. Savarino V, Di Mario F, Scarpignato C. Proton pump inhibitors in GORD. An overview of their pharmacology, efficacy and safety. Pharmacol Res 2009; 59: 135-153.
7. Sigterman KE, van Pinxteren B, Bonis PA, Lau J, Numans ME. Short-term treatment with proton pump inhibitors, H2-receptor antagonists and prokinetics for gastro-oesophageal reflux disease-like symptoms and endoscopy negative reflux disease. Cochrane Database of Systematic Reviews 2013, Issue 5. Art. No.: CD002095. DOI: 10.1002/14651858.CD002095.pub5.
8. Khan M, Santana J, Donnellan C, Preston C,Moayyedi P.Medical treatments in the short term management of reflux oesophagitis. Cochrane Database Syst Rev 2007:2. CD003244.
9. McDonagh MS, Carson S, Thakurta S. Drug Class Review: Proton Pump Inhibitors: Final Report Update 5 [Internet] Portland (OR): Oregan Health & Science University; 2009 [updated May 2009]. Available from: http://www.ncbi.nlm.nih.gov.ezproxy.utas.edu.au/books/NBK47260/pdf/TOC.pdf.
10. Preventing NSAID-induced ulcers in Therapeutic Guidelnes. Gastrointestinal Version 5, 2011, Melbourne.
11. Joo MK, Park CH, Kim JS, Park JM, Ahn JY, Lee BE, et al. Clinical Guidelines for Drug-Related Peptic Ulcer, 2020 Revised Edition. Gut Liver. 2020;14(6):707-26.
12. Wilhelm SM, Rjater RG, Kale-Pradhan PB. Perils and pitfalls of long-term effects of proton pump inhibitors. Expert Rev Clin Pharmacol 2013; 6(4): 443-451.
13. Thomson ABR, Sauve MD, Kassam N, Kamitakahara H. Safety of long-term use of proton pump inhibitors. World Journal of Gastroenterology 2010 16(19): 2323-2330.
14. Schoenfeld A, Grady D. Adverse Effects Associated With Proton Pump Inhibitors. JAMA Intern Med. Published online January 11, 2016. doi:10.1001/jamainternmed.2015.7927.
15. Antoniou T, Macdonald EM, Hollands S, et al. Proton pump inhibitors and the risk of acute kidney injury in older patients: a population-based cohort study. CMAJ Open. 2015;3(2):E166-E171. doi:10.9778/cmajo.20140074.
16. Lazarus B, Chen Y, Wilson FP, et al. Proton Pump Inhibitor Use and the Risk of Chronic Kidney Disease. JAMA Intern Med. Published online January 11, 2016. doi:10.1001/jamainternmed.2015.7193.
17. Tran-Duy A, Connell NJ, Vanmolkot FH, Souverein PC, de Wit NJ, Stehouwer CDA, et al. Use of proton pump inhibitors and risk of iron deficiency: a population-based case-control study. J Intern Med. 2019;285(2):205-14. Epub 2018/08/25. doi: 10.1111/joim.12826. PubMed PMID: 30141278.
18. Jung SB, Nagaraja V, Kapur A, Eslick GD. Association between vitamin B12 deficiency and long-term use of acid-lowering agents: a systematic review and meta-analysis. Int Med J 2015. Doi:10.1111/imj.12697.
19. Lam JR, Schneider JL, Zhao W, Corley DA. Proton pump inhibitor and histamine 2 receptor antagonist use and vitamin B12 deficiency. Jama. 2013;310(22):2435-42. Epub 2013/12/12. doi: 10.1001/jama.2013.280490. PubMed PMID: 24327038.
20. Cheungpasitporn W, Thongprayoon C, Kittanamongkolchai W, et al. Proton pump inhibitors linked to hypomagnesemia: a systematic review and meta-analysis of observational studies. Ren Fail. 2015;37(7):1237-1241.
21. Begley J, Smith T, Barnett K, Strike P, Azim A, Spake C, Richardson T. Proton Pump Inhibitor Associated Hypomagnesaemia - A Cause for Concern? Br J Clin Pharmacol. 2015 Nov 27. doi: 10.1111/bcp.12846. [Epub ahead of print]
22. Biswal S. Proton Pump Inhibitors and Risk for Clostridium difficile associated diarrhea. Biomed J 2014; 37: 178-183.
23. Kwok CS, Arthur AK, Anibueze CI, Singh S, Cavallazzi R, Loke YK. Risk of Clostridium difficile infection with acid suppressing drugs and antibiotics: meta-analysis. Am J Gastroenterol. 2012;107(7):1011-1019.
24. McDonald EG, Milligan J, Frenette C, Lee TC. Continuous proton pump inhibitor therapy and the associated risk of recurrent clostridium difficile infection. JAMA Intern Med 2015; 175 (5): 784-791.
25. Eom CS, Jean CY, Lim JW, Cho EG, Park SM, Lee KS. Use of acid-supressive drugs and risk of pneumonia: a systematic review and meta-anaylsis. CMAJ 2011; 183(3): 310-319.
26. Giuliano C, Wilhelm SM, Kale-Prahan PB. Atre proton pump inhibitors associated with development of community-acquired pneumonia" A meta-analysis. Expert Rev Clin Pharmacol 2012; 5(3): 337-344.
27. Herzig SJ, Howell MD, Ngo LH, Marcantonio ER. Acid-suppressive medication use and the risk for hospital-acquired pneumonia. Jama. 2009;301(20):2120-8.
28. Filion KB, Chateau D, Targownik LE, Gershon A, Durand M, Tamim H, Teare GF, Ravani P, Ernst P, Dormuth CR; CNODES Investigators. Proton pump inhibitors and the risk of hospitalisation for community-acquired pneumonia: replicated cohort studies with meta-analysis. Gut. 2014 Apr;63(4):552-8. doi: 10.1136/gutjnl-2013-304738. Epub 2013 Jul 15.
29. Hinson AM, Wilkerson BM, Rothman-Fitts I, Riggs AT, Stack BC, Bodenner DL. Hyperparathyroidism Associated with Long-Term Proton Pump Inhibitors Independent of Concurrent Bisphosphonate Therapy in Elderly Adults. J Am Geriatr Soc 63:2070–2073, 2015.
30. Zhou B, Huang Y, Li H, Sun W, Liu J. Proton-pump inhibitors and risk of fractures: an update meta-analysis. Osteoporos Int. 2016; 27: 339-347.
31. Waldum HL, Qvigstad G, Fossmark R, Kleveland PM, Sandvik AK. Rebound acid hypersecretion from a physiological, pathophysiological and clinical viewpoint. Scand J Gastroenterol 2010;45:389–94.
32. Rochoy M, Dubois S, Glantenet R, Gautier S, Lambert M. [Gastric acid rebound after a proton pump inhibitor: Narrative review of literature]. Therapie. 2018;73(3):237-46. Epub 2017/12/03. doi: 10.1016/j.therap.2017.08.005. PubMed PMID: 29195714.

AUTHORSHIP

This guide was prepared for Primary Health Tasmania by Stewart Mearns and reviewed by Angus Thompson, Pharmacist Clinical Editor, Primary Health Tasmania, the Deprescribing Project Advisory Group and Dr David Dunbabin, Geriatrician.

DEPRESCRIBING PROJECT ADVISORY GROUP

Nicole Bonner, Clinical Nurse, Masonic Care Tasmania

Dr Elizabeth Monks, Aged Care General Practitioner

Debbie Rigby, Consultant Pharmacist

Dr Andrew Stafford, Senior Lecturer, Curtin Medical School

Dr Joanne Stewart, General Practitioner

DECEMBER 2022