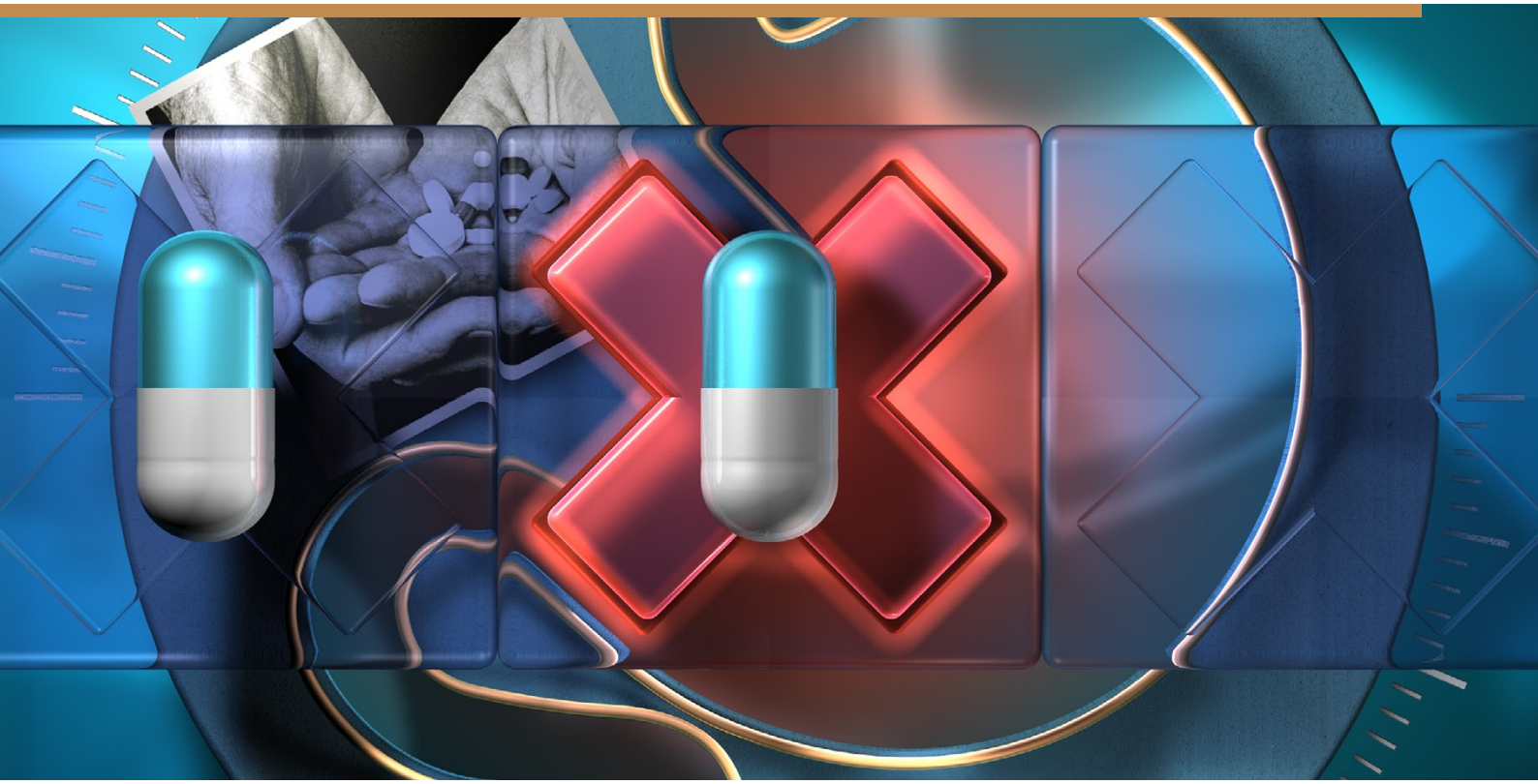


Stopping proton pump inhibitors in older people

Over one-third of people aged 65 years and older in New Zealand were dispensed a proton pump inhibitor (PPI) in the last year. PPIs are generally well tolerated; however, long-term treatment can be associated with an increased risk of adverse outcomes. PPIs should be used only when there is a specific clinical indication, and at the lowest effective dose for the shortest period of time. When appropriate, PPI treatment may be stepped down to a lower dose, used as needed only or stopped completely.

KEY MESSAGES:

- Proton pump inhibitors (PPIs) are highly effective medicines for preventing and treating conditions related to gastric acid secretion, e.g. gastro-oesophageal reflux disease (GORD), gastric and duodenal ulcers associated with use of non-steroidal anti-inflammatory drugs (NSAIDs) or *Helicobacter pylori* infection
- Long-term PPI treatment is associated with a small increase in the risk of adverse outcomes, including bone fractures, malabsorption of nutrients (e.g. vitamin B12, magnesium, iron) and increased susceptibility to some bacterial infections
- Regularly review PPI use to determine whether long-term treatment is still indicated, or whether a lower dose or stopping completely could be trialled
- If stopping the PPI is appropriate, a "step-down" approach is recommended, e.g. reduce the dose, use every second day or as needed, and then stop completely
- Patients should be warned about the possibility of rebound symptoms and how to manage these, when stopping PPIs

What are proton pump inhibitors (PPIs)?

Proton pump inhibitors (PPIs) prevent the final step of gastric acid secretion by blocking the hydrogen/potassium adenosine triphosphatase (H^+/K^+ ATPase) enzyme, i.e. the "proton pump", in the parietal cells in the stomach. PPIs are indicated for the prevention and treatment of the following conditions related to gastric acid secretion:[1]

- Gastro-oesophageal reflux disease (GORD) and associated complications, e.g. erosive oesophagitis, Barrett's oesophagus
- Gastric and duodenal ulcers associated with non-steroidal anti-inflammatory drug (NSAID) treatment
- Eradication of *Helicobacter pylori* (in combination with an antibiotic)
- Zollinger–Ellison syndrome

For further information on PPIs, see: **www.bpac.org.nz/BPJ/2014/June/ppi.aspx**

Which PPIs are available in New Zealand?

There are currently three fully subsidised PPIs available in New Zealand: omeprazole, pantoprazole and lansoprazole. Omeprazole and pantoprazole can also be purchased in limited quantities as "Pharmacist Only" medicines at a maximum dose of 20 mg. Rabeprazole is also available with a prescription but is not subsidised.

All of the PPIs available in New Zealand have a similar efficacy when used at the recommended dose for the treatment of GORD and erosive oesophagitis.[2–4] There is some variability between the PPIs in terms of their indications, e.g. only omeprazole and pantoprazole are indicated for the prevention of NSAID-associated ulcers and the treatment of Zollinger-Ellison syndrome, in addition to their other indications.[4] The adverse effect profile is similar for the different PPIs available in New Zealand.[1]

For further information on the indications for a specific PPI, refer to the New Zealand Formulary: **www.nzf.org.nz**

PPIs are widely used by older adults in New Zealand

In 2018, omeprazole was the third most commonly dispensed medicine in New Zealand, after paracetamol and atorvastatin.[5] In the 12 months from July, 2017 to June, 2018, approximately 243,000 people aged 65 years and older (34% of this population) were dispensed a PPI.[6] Four times more prescriptions were dispensed for omeprazole than for pantoprazole and lansoprazole combined.[6] The highest number of prescriptions for omeprazole were dispensed to people aged over 80 years, with 339 dispensed prescriptions per 1,000 registered patients in this group compared to 242 dispensed prescriptions in people aged 65 to 69 years.[6]

Evidence-based indications for PPI use in older adults

Gastro-oesophageal reflux disease (GORD)

The prevalence of GORD increases with age, which may be explained by age-related functional changes to the lower oesophageal sphincter, decreased salivary bicarbonate secretion or the use of medicines that affect sphincter tone, e.g. nitrates, calcium channel blockers, benzodiazepines, anticholinergics and antidepressants.[7,8] The frequency of the typical symptoms of GORD, i.e. heartburn and acid regurgitation, may be reduced in older people, while the presence of atypical symptoms may be increased, e.g. nausea, vomiting, anorexia, dysphagia, respiratory symptoms, belching, dyspepsia, hoarseness, post-prandial fullness.[8,9] Older people are more likely to experience complications associated with GORD, e.g. erosive oesophagitis, oesophageal stricture (narrowing of the oesophagus), Barrett's oesophagus and oesophageal cancer.[8,9]

Typically, a short-course of treatment with a PPI, i.e. four to eight weeks, is recommended to provide relief from the symptoms of GORD and allow healing of any associated oesophageal lesions.[1,10,11] A meta-analysis of seven studies including over 3,000 people found that PPIs provided better relief from heartburn than histamine H_2-receptor antagonists (relative risk = 0.66; 95% confidence interval (CI) = 0.60–0.73).[12]

The expected duration of treatment should be discussed with patients when initiating a PPI so they are aware that it is intended for short-term use. Ongoing treatment may be indicated if symptom resolution has not been achieved or for patients with complications associated with GORD.[13]

For further information on the use of PPIs for the management of GORD, see: **www.bpac.org.nz/bpj/2014/june/gord.aspx**

Protection from upper gastrointestinal (GI) tract adverse events associated with NSAID treatment. NSAIDs increase the risk of gastric or duodenal ulceration and bleeding when used long-term as they reduce the production of gastric mucus which provides protection against erosion by gastric acid.[14] PPIs can be prescribed prophylactically to people who require NSAIDs, including aspirin, long-term and have risk factors for gastrointestinal ulceration or bleeding.[1,13–15] A meta-analysis of 18 studies including over 9,000 people found that concurrent PPI treatment significantly reduced the risk of ulcers in people who were taking NSAIDs (odds ratio = 0.23; 95% CI = 0.19–0.27).[16]

Risk factors for GI complications associated with long-term NSAID treatment include:[15]

- Age > 65 years
- History of gastric or duodenal ulcers or bleeding
- Use of other medicines which increase the risk of GI adverse events, e.g. anticoagulants, aspirin, selective serotonin reuptake inhibitors (SSRIs), corticosteroids
- Co-morbidities, e.g. cardiovascular disease, diabetes, renal or hepatic impairment
- Lifestyle factors, e.g. smoking, excess alcohol consumption

N.B. The use of NSAIDs, including COX-2 inhibitors, is contraindicated in people who have active GI ulceration or bleeding or a history of NSAID-associated GI complications.[1] If possible, NSAIDs should be avoided in people with a history of ulceration or bleeding.[1]

For further information on NSAIDs, see: **www.bpac.org.nz/BPJ/2013/October/nsaids.aspx**

For further information on the COX-2 inhibitor, celecoxib, see: **www.bpac.org.nz/2018/celecoxib.aspx**

Treatment of gastric and duodenal ulcers and bleeding. If left untreated, the complications associated with ulceration, i.e. bleeding and perforation, are associated with increased mortality.[13] Treatment with a PPI for four to eight weeks is recommended to allow healing of gastric and duodenal ulcers.[1] A meta-analysis of 24 studies including over 2,500 people found that PPI treatment significantly improved ulcer healing when compared to controls* (odds ratio = 5.22; 95% CI, = 4.00–6.80).[16]

* People receiving a placebo or no treatment

Treatment of *Helicobacter pylori* infection. *H. pylori* infection causes inflammation of the mucosal layer underlying the epithelial lining of the stomach.[18] Some people infected with *H. pylori* may be asymptomatic, while others may develop gastric or duodenal ulceration or bleeding.[18] *H. pylori* infection can lead to cancer in the distal (non-cardia) body of the stomach.[18] People of Pacific or Māori ethnicity have an increased risk (3.4 times and 1.9 times, respectively) of *H. pylori* infection compared to people of European ethnicity, which may contribute to the higher rates of gastric cancer in these groups.[19, 20]

For patients who have confirmed *H. pylori* infection, e.g. on a faecal antigen test, one week of eradication treatment with an antibiotic regimen and PPI is recommended.[1]

For further information on testing for H. pylori, see: **www.bpac.org.nz/BT/2014/May/h-pylori.aspx**

The risks of PPI use in older adults

PPIs are generally well tolerated when used short-term. The most common adverse effects are headaches or GI disturbances, e.g. diarrhoea or constipation, however, symptoms are usually mild. PPIs may interact with other medicines by altering their absorption or hepatic metabolism, however, in general, this has little clinical significance. Older people can be more susceptible to the effects of medicine interactions due to the presence of frailty and/or the use of multiple medicines. Dose adjustments or switching to another type of PPI may be appropriate for some patients.

To check for specific medicine interactions with PPIs, refer to the New Zealand Formulary: **www.nzf.org.nz**

Long-term PPI use has been associated with an increased risk of several adverse outcomes in observational studies, including bone fractures, vitamin B12, magnesium or iron deficiency, *Clostridium difficile* infection and community-acquired pneumonia.[13, 22] While causality has not been established and the absolute risk of these adverse effects is generally

PPI treatment can mask the symptoms of oesophageal or gastric cancer

Acid-suppressing medicines such as PPIs can mask the symptoms of upper GI cancers, e.g. oesophageal or gastric cancer. People who present with dyspepsia, including epigastric pain or discomfort, heartburn or regurgitation, with or without bloating, nausea or vomiting, and have red flags (see below) should be referred for endoscopy.[21]

Red flags for oesophageal and gastric cancer include:[21]

- Aged ≥ 50 years at first presentation for people of European ethnicity; aged ≥ 40 years at first presentation for people of Māori, Pacific or Asian ethnicity
- Family history of gastric cancer
- GI bleeding
- Iron deficiency anaemia
- Difficulty swallowing
- Persistent vomiting
- Palpable abdominal mass
- Unexplained weight loss

Adverse effects associated with long-term PPI use

The risks associated with long-term PPI use include:[13]

Bone fractures. A meta-analysis of 18 observational studies including over 240,000 fracture cases found that PPI use was associated with a 33% increase in the relative risk for a fracture at any site.[23] Fractures of the hip and spine were associated with a relative risk increase of 26% and 58%, respectively.[23] The absolute risk increase for a bone fracture is estimated to be 0.1% to 0.5% per year for an individual patient.[13]

Malabsorption of nutrients. Gastric acidity is important for the absorption of dietary protein-bound vitamin B12 and minerals ingested as salts, e.g. calcium, iron, magnesium.[13] A meta-analysis of five studies found a significant association between use of an acid-lowering medicine, i.e. PPIs or histamine receptor 2 antagonists, for ten months or longer and vitamin B12 deficiency (hazard ratio = 1.83; 95% CI = 1.36–2.46).[22] Observational studies have reported an increased risk of hypomagnesaemia in patients taking PPIs (pooled relative risk = 1.43; 95% CI = 1.08–1.88).[24] A case-controlled study of over 450,000 people in the United States found that PPI use for two or more years was associated with iron deficiency (adjusted odds ratio = 2.49; 95% CI = 2.35–2.64).[25] This was a dose dependent effect and the association decreased when the medicine was stopped.[25] Acid suppression by PPIs may reduce the absorption of insoluble calcium salts, e.g. calcium carbonate.[26] However, if dietary calcium intake is adequate, this should only be a minor effect.[26] Absorption of soluble calcium salts, e.g. calcium citrate, or calcium absorption from milk and cheese are unaffected by gastric pH.[26]

***Clostridium difficile* infection.** The acid-lowering effect of PPIs can promote *C. difficile* proliferation in the large intestine, leading to diarrhoea.[9] The relative risk for community-acquired *C. difficile* infection is increased by 50% in people taking PPIs, however, the low incidence of this bacterial infection means the absolute risk increase is estimated to be 0.09% per year.[13]

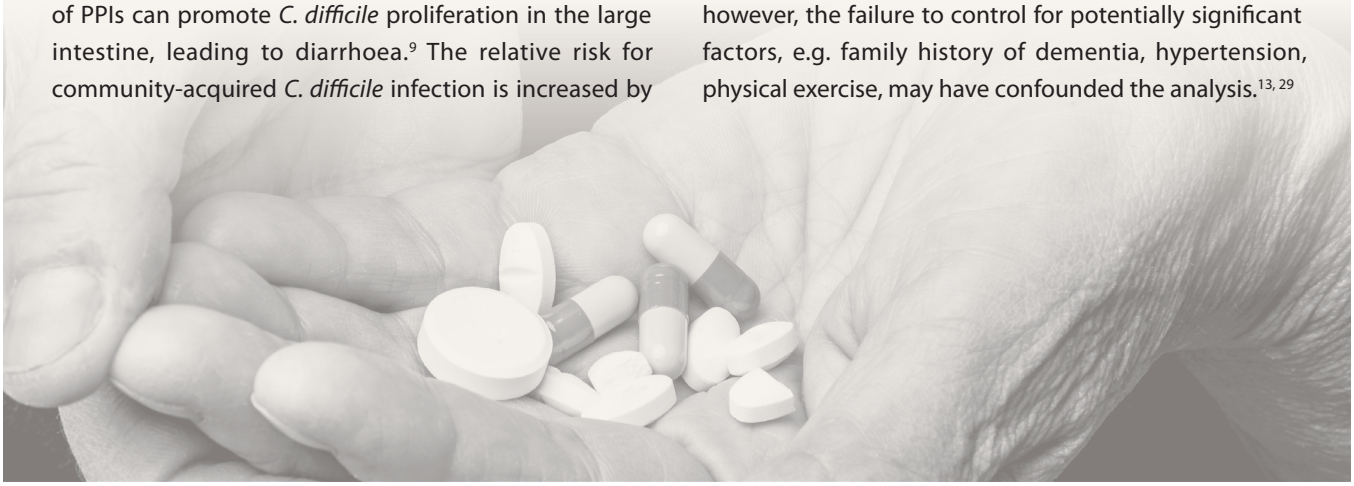
Community-acquired pneumonia. The acid-lowering effects of PPIs is thought to allow proliferation of bacteria in the stomach, which may then move up into the oesophagus to be aspirated and cause lower respiratory tract infection, e.g. pneumonia.[22] A study of over 75,000 people aged 60 years and older in primary care in the United Kingdom found there was a significant association between PPI use longer than one year and pneumonia (adjusted hazard ratio = 1.82; 95% confidence interval (CI) = 1.27–2.54).[27]

Chronic kidney disease. PPI use has been associated with chronic kidney disease and end-stage renal disease.[28] A meta-analysis of five studies* including over 600,000 people reported that the risk of chronic kidney disease and end-stage renal disease were 16% and 39% higher, respectively, in people taking PPIs compared to those who did not.[28] The risk of chronic kidney disease increased with the duration of PPI treatment.[28] The estimated absolute risk increase of chronic kidney disease for an individual patient per year is 0.1% to 0.3%.[13]

* Adjustment for confounding factors, including concurrent NSAID treatment, differed between the studies included in this meta-analysis.

For further information on PPIs and acute interstitial nephritis and acute kidney injury, see: **www.bpac.org.nz/BPJ/2016/July/update.aspx**

Dementia. The association between PPI use and dementia is unclear. Some studies have reported an increased risk, however, the failure to control for potentially significant factors, e.g. family history of dementia, hypertension, physical exercise, may have confounded the analysis.[13, 29]



considered to be low (see: "Adverse effects associated with long-term PPI use), each practice is likely to have a number of patients taking PPIs, some of whom may be more susceptible to these adverse outcomes due to co-morbidities, medicines use or the presence of frailty.

Managing the risks associated with long-term PPI treatment

Fracture risk. Some older people taking PPIs may be more vulnerable to fractures than others, e.g. increased risk of falls due to frailty. Ensure that patients with risk factors for osteoporosis maintain adequate vitamin D and calcium intake, and that strategies to reduce the risk of falls are in place, e.g. avoiding medicines associated with a risk of falls and/or recommending exercises to improve strength and balance, the use of walking aids and installing hand rails at home.

For further information on frailty and falls, see: **www.bpac.org.nz/2018/frailty.aspx**

For further information on osteoporosis, see: **www.osteoporosis.org.nz/clinical-guidance/**

Nutrient deficiencies. A balanced diet including foods that contain vitamin B12, magnesium and iron should be sufficient to avoid nutrient deficiencies for most people taking a PPI long-term, and routine monitoring of magnesium or vitamin B12 levels is not recommended.[13] If patients are not able to meet their daily intake requirements of these nutrients through diet alone, supplementation may be appropriate.

For further information on hypomagnesaemia associated with PPI use, see: **www.bpac.org.nz/BPJ/2013/April/hypomagnesaemia.aspx**

Infection risk. While the increased absolute risk of *C. difficile* infection is low, other factors such as recent antibiotic exposure and hospitalisation add to this risk.[22] Evaluation of the risk versus benefit of long-term PPI treatment should be considered for patients with multiple risk factors.[22] Encourage pneumococcal vaccination for all older people, including those taking PPIs long-term.

Reviewing long-term PPI use

PPI use should be periodically reviewed to determine whether long-term use is still indicated. For people who are taking multiple medicines, stopping unnecessary treatment with a PPI has the added benefit of reducing the number of medicines they are taking, i.e. the "pill burden", and may improve adherence to their regimen of medicines that are necessary.

An audit of PPI prescribing for general practitioners can be found here: (link to the new PPI audit)

Consider whether stopping is appropriate

It may be appropriate to discontinue PPI treatment in some patients, such as:[10]

- Patients who have been taking a PPI for a minimum of four weeks and have had a complete resolution of their symptoms
- Where the risks associated with ongoing treatment outweigh the benefits (negative risk/benefit ratio)
- Where ongoing use is not indicated, e.g. prescribed for ulcer prophylaxis and the NSAID has been stopped

For some patients, long-term treatment with a PPI is indicated and withdrawal of the medicine is not appropriate, e.g. Barrett's oesophagus, chronic NSAID treatment or erosive, ulcerative or stricturing (narrowing of the oesophagus) GORD that has been confirmed by endoscopy.[1, 13] However, periodic review of PPI treatment is recommended to ensure that the lowest effective dose is being used to manage their symptoms.[13]

Remind patients about lifestyle strategies for managing GORD symptoms

Lifestyle strategies that can help to minimise reflux symptoms include:[10, 30]

- Weight loss for people who are obese or overweight
- Smoking cessation
- Avoiding foods that exacerbate symptoms, e.g. alcohol, coffee, and spicy, fatty or acidic foods
- Eating smaller meals and avoiding meals three to four hours before bedtime
- Elevating the head of the bed, but without using extra pillows as this may worsen symptoms by increasing intra-abdominal pressure
- Relaxation to reduce stress and anxiety

Stepping down PPIs

A "step down" approach may be considered for people who have been prescribed a PPI, are no longer experiencing symptoms and/or where withdrawing the PPI is appropriate, i.e. long-term PPI treatment is not required. Stepping down involves gradually reducing the dose over time, e.g. two to four weeks, before stopping the medicine completely.

Inform patients about possible rebound symptoms

Stopping PPI treatment can cause rebound acid hypersecretion, leading to the transient appearance of symptoms such as indigestion, heartburn or regurgitation.[31] The low-acid environment induced by PPI treatment increases gastrin production (hypergastrinaemia) in order to stimulate gastric acid secretion and decrease the gastric pH.[31] When the PPI

is withdrawn, there is no longer a mechanism to suppress gastric acid secretion and this increase in acidity causes rebound symptoms which are often indistinguishable from the symptoms of GORD.[31] The process of stepping down should help to minimise these symptoms, particularly if used alongside lifestyle modifications (see: "Lifestyle strategies for managing GORD symptoms"). Other treatments may also be used in the short-term to help manage these rebound symptoms, e.g. a histamine H_2 receptor antagonist or an antacid/alginate (see: "Stepping down PPIs").[10]

It is difficult to predict how long the acid rebound effects might last and it likely relates to the length of time the patient was taking a PPI.[32] Data from a small study carried out in the United States found that gastrin levels normalised within the first month of discontinuing PPI treatment in patients who had been taking a PPI for four or eight weeks.[24]

A stepping down protocol

There are several approaches to stepping down PPI treatment and there is no evidence that one protocol is superior to another.[10] The process of withdrawing a PPI should be individualised to the patient and guided by the presence or absence of symptoms at each step. Some patients may only require one step down before they can stop their PPI, others may require several steps down and the use of other treatments to manage rebound symptoms. Some patients may continue to use a PPI as needed for the occasional symptoms of GORD.[10, 13]

A protocol for stepping down can be carried out over two to four weeks as follows:[1, 10, 32]

Step 1: Establish the patient's regular PPI requirements

Step 2: Halve the daily dose of the PPI or change the frequency of dosing, e.g. from twice daily to once daily or from daily use to alternate days. Patients who have been on a high dose are likely to require a second or third step-down to reach the lowest dose, e.g. 10 mg on alternate days.

Step 3: Stop the PPI

If at any stage during the step-down process, or after stopping, acid reflux symptoms occur, trial a histamine H_2-receptor antagonist, e.g. ranitidine, 150 mg twice daily,* or an antacid, e.g. aluminium hydroxide tablets, or a medicine that contains an antacid and an alginate.†

Histamine H_2-receptor antagonists decrease the secretion of gastric acid by inhibiting the action of histamine at the H_2 receptors on gastric parietal cells. These medicines are generally less effective than PPIs for the long-term management of GORD as they only block one of the pathways involved in the stimulation of gastric acid secretion, however, they may provide short-term relief in patients who are stopping PPI treatment and are experiencing mild rebound symptoms.[12] H_2-receptor antagonists can cause adverse reactions affecting the central nervous system that older people in particular may be more susceptible to, e.g. headache, dizziness confusion or delirium.[8]

Antacids neutralise stomach acid, while **alginates** form a viscous raft that floats on the stomach contents.[1] Antacids that contain an anti-foaming agent, e.g. aluminium hydroxide in combination with simeticone, may also provide relief from the symptoms of heartburn and indigestion.[1]

If despite these measures, symptoms persist, e.g. more than three times per week or for longer than one month, and are affecting the patient's quality of life, consider returning to the previous PPI dose and if appropriate, testing for H. pylori.[10]

* Half the normal dose is recommended for patients with renal impairment, refer to the New Zealand Formulary for further details: **www.nzf.org.nz**

† Acidex contains an antacid and alginate and is available partially subsidised. The high sodium content in some of these medicines may not be suitable for patients with renal or hepatic impairment, refer to the New Zealand Formulary for further details: **www.nzf.org.nz**

References

1. New Zealand Formulary (NZF). NZF v78. 2018. Available from: www.nzf.org.nz (Accessed Dec, 2018).
2. Caro JJ, Salas M, Ward A. Healing and relapse rates in gastroesophageal reflux disease treated with the newer proton-pump inhibitors lansoprazole, rabeprazole, and pantoprazole compared with omeprazole, ranitidine, and placebo: evidence from randomized clinical trials. Clin Ther 2001;23:998–1017.
3. Wang W-H, Huang J-Q, Zheng G-F, et al. Head-to-head comparison of H2-receptor antagonists and proton pump inhibitors in the treatment of erosive esophagitis: a meta-analysis. World J Gastroenterol 2005;11:4067–77.
4. Zhang C, Kwong JSW, Yuan R-X, et al. Effectiveness and tolerability of different recommended doses of PPIs and H2RAs in GERD: network meta-analysis and GRADE system. Sci Rep 2017;7:41021. doi:10.1038/srep41021
5. bpacnz. Annual practice report - pharmaceutical utilisation July, 2017 - June, 2018. 2018. Available from: https://bpac.org.nz/report/2018/AnnualReport2018_SampleGPReport.pdf (Accessed Dec, 2018).
6. Ministry of Health. Pharmaceutical Claims Collection. 2018.
7. Yamasaki T, Hemond C, Eisa M, et al. The changing epidemiology of gastroesophageal reflux disease: are patients getting younger? J Neurogastroenterol Motil 2018;24:559–69. doi:10.5056/jnm18140
8. Chait MM. Gastroesophageal reflux disease: Important considerations for the older patients. World J Gastrointest Endosc 2010;2:388–96. doi:10.4253/wjge.v2.i12.388
9. Johnson DA, Fennerty MB. Heartburn severity underestimates erosive esophagitis severity in elderly patients with gastroesophageal reflux disease. Gastroenterology 2004;126:660–4.
10. Farrell B, Pottie K, Thompson W, et al. Deprescribing proton pump inhibitors: evidence-based clinical practice guideline. Can Fam Physician 2017;63:354–64.
11. National Institute for Health and Care Excellence. Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management. 2014. Available from: https://www.nice.org.uk/guidance/cg184/chapter/appendix-a-dosage-information-on-proton-pump-inhibitors (Accessed Nov, 2018).
12. Sigterman KE, van Pinxteren B, Bonis PA, et al. 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 Syst Rev 2013;:CD002095. doi:10.1002/14651858.CD002095.pub5
13. Freedberg DE, Kim LS, Yang Y-X. The risks and benefits of long-term use of proton pump inhibitors: expert review and best practice advice from the American Gastroenterological Association. Gastroenterology 2017;152:706–15. doi:10.1053/j.gastro.2017.01.031
14. Gwee KA, Goh V, Lima G, et al. Coprescribing proton-pump inhibitors with nonsteroidal anti-inflammatory drugs: risks versus benefits. J Pain Res 2018;11:361–74. doi:10.2147/JPR.S156938
15. Day RO, Graham GG. Non-steroidal anti-inflammatory drugs (NSAIDs). BMJ 2013;346:f3195. doi:10.1136/bmj.f3195
16. Scally B, Emberson JR, Spata E, et al. Effects of gastroprotectant drugs for the prevention and treatment of peptic ulcer disease and its complications: a meta-analysis of randomised trials. Lancet Gastroenterol Hepatol 2018;3:231–41. doi:10.1016/S2468-1253(18)30037-2
17. Lau JY, Sung J, Hill C, et al. Systematic review of the epidemiology of complicated peptic ulcer disease: incidence, recurrence, risk factors and mortality. Digestion 2011;84:102–13. doi:10.1159/000323958
18. Mitchell H, Katelaris P. Epidemiology, clinical impacts and current clinical management of Helicobacter pylori infection. Med J Aust 2016;204:376–80.
19. McDonald AM, Sarfati D, Baker MG, et al. Trends in Helicobacter pylori infection among Māori, Pacific, and European Birth cohorts in New Zealand. Helicobacter 2015;20:139–45. doi:10.1111/hel.12186
20. Ellison-Loschmann L, Sporle A, Corbin M, et al. Risk of stomach cancer in Aotearoa/New Zealand: A Māori population based case-control study. PLOS ONE 2017;12:e0181581. doi:10.1371/journal.pone.0181581
21. New Zealand Guidelines Group. Suspected cancer in primary care: guidelines for investigation, referral and reducing ethnic disparities. 2009. Available from: https://www.health.govt.nz/system/files/documents/publications/suspected-cancer-guideline-sep09.pdf (Accessed Dec, 2018).
22. Maes ML, Fixen DR, Linnebur SA. Adverse effects of proton-pump inhibitor use in older adults: a review of the evidence. Ther Adv Drug Saf 2017;8:273–97. doi:10.1177/2042098617715381
23. Zhou B, Huang Y, Li H, et al. Proton-pump inhibitors and risk of fractures: an update meta-analysis. Osteoporos Int 2016;27:339–47. doi:10.1007/s00198-015-3365-x
24. 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;37:1237–41. doi:10.3109/0886022X.2015.1057800
25. Lam JR, Schneider JL, Quesenberry CP, et al. Proton pump inhibitor and histamine-2 receptor antagonist use and iron deficiency. Gastroenterology 2017;152:821-829.e1. doi:10.1053/j.gastro.2016.11.023
26. Yang Y-X. Chronic PPI therapy and calcium metabolism. Current Gastroenterology Reports 2012;14:473–9. doi:10.1007/s11894-012-0290-4
27. Zirk-Sadowski J, Masoli JA, Delgado J, et al. Proton-pump inhibitors and long-term risk of community-acquired pneumonia in older adults. J Am Geriatr Soc 2018;66:1332–8. doi:10.1111/jgs.15385
28. Sun J, Sun H, Cui M, et al. The use of anti-ulcer agents and the risk of chronic kidney disease: a meta-analysis. Int Urol Nephrol 2018;50:1835–43. doi:10.1007/s11255-018-1908-8
29. Batchelor R, Gilmartin JF-M, Kemp W, et al. Dementia, cognitive impairment and proton pump inhibitor therapy: A systematic review. J Gastroenterol Hepatol 2017;32:1426–35. doi:10.1111/jgh.13750
30. National Institute for Health and Care Excellence. Dyspepsia - proven GORD. 2017. Available from: https://cks.nice.org.uk/dyspepsia-proven-gord#!scenario (Accessed Nov, 2018).
31. Waldum HL, Qvigstad G, Fossmark R, et al. Rebound acid hypersecretion from a physiological, pathophysiological and clinical viewpoint. Scand J Gastroenterol 2010;45:389–94. doi:10.3109/00365520903477348
32. Kim J, Blackett JW, Jodorkovsky D. Strategies for effective discontinuation of proton pump inhibitors. Curr Gastroenterol Rep 2018;20:27. doi:10.1007/s11894-018-0632-y

This article is available online at:
www.bpac.org.nz/2019/xxx.aspx