Proton Pump Inhibitors
in Primary Care

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Proton Pump Inhibitors (PPIs) are widely prescribed medications. Over a 12 month period in 2013-14, more than 375,000 people in British Columbia received a prescription for a PPI.[1] They are efficacious medications, particularly for: gastroesophageal reflux disease (GERD), reflux esophagitis, and *Helicobacter pylori*-associated peptic ulcer disease. While PPIs are often viewed as having relatively few short term adverse events, signals of harm from observational studies reinforce that it is prudent to clarify the therapeutic intent and duration of all PPI prescriptions.

PAD's educational session, *Proton Pump Inhibitors*, aims to offer clinicians an opportunity to discuss the following:

- Which primary care PPI indications are adequately studied for patient centered outcomes?
- What evidence is there for potential harms associated with PPI therapy?
- Is one PPI more efficacious than another?
- Are higher doses of PPIs more efficacious than 'standard' doses?
- When are patients with GERD and other dyspeptic symptoms likely to respond to PPI therapy?

Clarify the therapeutic intent of PPI therapy and ensure there is a compelling indication

Observational studies have identified possible associations between PPIs and clinically important adverse events (e.g., Clostridium difficile infection).[2-9]

Give attention to the cost of PPI therapy

Therapeutic reviews do not identify high quality evidence of clinically important differences between PPIs.[10-14] However there are large differences in cost.

More is not necessarily better

Comparisons of once daily, high doses of PPIs versus once daily, standard doses of PPIs have not demonstrated consistent and clinically important benefits with the higher doses (e.g., as initial therapy in GERD or reflux esophagitis).[10,12-16]

Make a decision early and assess for the opportunity to taper

Improvement in GERD and other dyspeptic symptoms is expected early for PPI responders. It is reasonable to make a decision regarding the adequacy of symptom improvement after 4 to 8 weeks of PPI therapy.[15,17-27]

What's Inside

2 Proton Pump Inhibitors (PPIs): Efficacy

Systematic Reviews: Common PPI Primary Care Indications	
Evidence for Gastrointestinal Outcomes	**Clinical Implications**
Uninvestigated gastroesophageal reflux disease (GERD)[28] Heartburn remission: PPI 72% vs. placebo 25%, **NNTB 2** high QOE PPI 55% vs. H2RA 32%, **NNTB 4** moderate QOE	o The evidence does not identify which patients with GERD symptoms would benefit most from a PPI vs. an H2RA (e.g., ranitidine) as initial therapy[28] o It is not known if PPI therapy affects the progression to possible complications associated with reflux esophagitis (e.g., peptic stricture, bleeding, ulceration, Barrett's esophagus, esophageal adenocarcinoma)[16,29] o There is currently insufficient evidence to establish a role for PPI therapy in the treatment of extra-esophageal GERD symptoms (e.g., nonspecific chronic cough, asthma, laryngeal symptoms)[10,12,30,31] o PPI therapy may improve symptoms in a small proportion of patients with functional (non-ulcer) dyspepsia but PPIs are not more effective than H2RAs[32] o Comparisons of once daily, high doses of PPIs vs. once daily, standard doses of PPIs have not demonstrated consistent and clinically important benefits with the higher doses (e.g., as initial therapy in GERD or reflux esophagitis)[10,12-16] o The efficacy and safety of twice daily PPI therapy is relatively unstudied for these primary care indications[19,33-35]
Reflux (erosive) esophagitis[15,16] Acute healing of erosive esophagitis: PPI 83% vs. placebo 28%, **NNTB 2*** PPI 80% vs. H2RA ± prokinetic 54%, **NNTB 4*** Maintenance of healed esophagus: PPI 78% vs. placebo 21%, **NNTB 2*** PPI 78% vs. H2RA 42%, **NNTB 3*** Maintenance of symptom relief: PPI 71% vs. placebo 24%, **NNTB 2*** PPI 78% vs. H2RA 56%, **NNTB 4***	
Endoscopy negative reflux disease[28] Heartburn remission: PPI 38% vs. placebo 13%, **NNTB 4** moderate QOE PPI 55% vs. H2RA 43%, **NNTB 8** low QOE	
Functional (non-ulcer) dyspepsia[32] Improvement in dyspepsia: PPI 34% vs. placebo 25%, **NNTB 10*** PPI 32% vs. H2RA 28%, **NSS***	
Helicobacter pylori* eradication (HPE) for peptic ulcer disease**[36] Duodenal ulcer recurrence: HPE 13% vs. placebo 67%, **NNTB 2 HPE 12% vs. maintenance ulcer healing drug 16%, **NSS*** Gastric ulcer recurrence: HPE 16% vs. placebo 50%, **NNTB 3***	o In *H. pylori* positive patients with peptic ulcer disease, eradication therapy decreases peptic ulcer recurrence compared to no treatment[36] o Prolonged PPI therapy (e.g., for 4 to 8 weeks) after a course of eradication therapy is not routinely recommended for uncomplicated duodenal ulcers but has been recommended for gastric ulcers or complicated duodenal ulcers[10,37-40] o Consult *Bugs & Drugs* for Canadian *H. pylori* recommendations[40]
Prevention of NSAID associated peptic ulcer[41] Endoscopic peptic ulcer: PPI 14% vs. placebo 36%, **NNTB 4*** PPI vs. H2RA: insufficient direct comparative data*	o The effect of PPI therapy on NSAID-associated peptic ulcer complications (e.g., bleeding, perforation, obstruction, death) has not been adequately established[41-44]
Prevention of antiplatelet associated (e.g., ASA, clopidogrel) peptic ulcer	o No comprehensive systematic review was identified to inform decision making

*Quality of the evidence is unclear: this systematic review does not assess the risks of bias of the included trials using current Cochrane methodology.[45]

% = proportion of participants with outcome; **NNTB** = numbers needed to treat to benefit; **QOE =** quality of the evidence (Cochrane authors' judgment); **H2RA** = histamine receptor antagonist (e.g., ranitidine); **prokinetic** e.g., metoclopramide, cisapride (cisapride removed from the Canadian market); **NSS** = not statistically significant; ***Helicobacter pylori* eradication (HPE)** = combination of antimicrobial and acid suppressive therapy (e.g., PPI, H2RA, bismuth subsalicylate) for at least 7 days; **ulcer healing drug** e.g., proton pump inhibitor, histamine receptor antagonist; **endoscopic peptic ulcer** = gastric or duodenal ulcer at least 3 mm in diameter and/or distinguishable from an erosion

Proton Pump Inhibitors (PPIs): Drug Information

Proton Pump Inhibitor	Rabeprazole (Pariet®, generics)[21]	Pantoprazole (Pantoloc®, Tecta®, generics)[22,23]	Omeprazole (Losec®, generics)[24]	Lansoprazole (Prevacid®, generics)[25]	Esomeprazole (Nexium®, generics)[26]	Dexlansoprazole (Dexilant®, generics)[27]
Standard Dose[10,16,35]	**20 mg once a day**	**40 mg once a day**	**20 mg once a day**	**30 mg once a day**	**20 mg once a day**	**30 mg once a day**
Oral Dosage Forms	Tablet: 10 mg, 20 mg	Tablet: 20 mg, 40 mg	Tablet: 10 mg, 20 mg Capsule: 10 mg, 20 mg	Capsule: 15 mg, 30 mg Disintegrating Tablet: 15 mg, 30 mg	Tablet: 20 mg, 40 mg Capsule: 20 mg, 40 mg Sachet: 10 mg	Tablet: 30 mg, 60 mg
Renal Impairment	No dose adjustment recommended	No dose adjustment recommended	No dose adjustment recommended	No dose adjustment recommended	No dose adjustment recommended	No dose adjustment recommended
Moderate Hepatic Impairment (Child-Pugh Class B)	No recommendation provided	No recommendation provided	No dose adjustment recommended	Maximum dose 30 mg per day	No dose adjustment recommended	Maximum dose 30 mg per day
Severe Hepatic Impairment (Child-Pugh Class C)	Consider dose reduction	Maximum dose 20 mg per day	Maximum dose 20 mg per day	Consider dose reduction	Maximum dose 20 mg per day	Not studied
Cost for 28 days	$3.64 (10 mg) **$7.28 (20 mg)**	$38.56 (20 mg) **$10.97 (40 mg)**	$24.69 (10 mg) **$12.45 (20 mg)**	$15.12 (15 mg) **$15.12 (30 mg)**	**$43.23 (20 mg)** $43.23 (40 mg)	**$66.64 (30 mg)** $66.64 (60 mg)
PharmaCare Coverage	Limited Coverage	Limited Coverage	Limited Coverage	Limited Coverage	Limited Coverage	No coverage

Notes:

- **Therapeutic reviews** do not identify high quality evidence of clinically important differences between PPIs in symptom relief or healing rates (i.e., for GERD, erosive esophagitis, treatment of peptic ulcer disease) or for *H. pylori* eradication.[10-14]
- **Once daily, standard doses are recommended as the initial PPI dose for most primary care indications.**[21-27]
- High dose esomeprazole (40 mg) and high dose dexlansoprazole (60 mg) are approved as an 8 week treatment course for acute healing of erosive esophagitis.[26,27] In the U.S., esomeprazole 20 mg is also recommended for this indication.[46]
- Greater than once daily, standard doses are recommended for gastric acid hypersecretory conditions (e.g., Zollinger Ellison Syndrome) and for *H. pylori* eradication therapy.[21-26]
- **Non-prescription PPI:** omeprazole 20 mg once a day (Olex®) approved by Health Canada for frequent heartburn (≥ 2 days per week) as a 14 day course of therapy which may be repeated every 4 months.[47]
- **Costs**: calculated from generic prices where available as of November 1, 2014; without professional fees or markup.[48] The costs of lansoprazole disintegrating tablets ($60.48 for 28 days) and esomeprazole sachets ($65.86 for 28 days) are significantly greater than that of the standard dosage forms.[48]
- **Limited Coverage:** Special Authority Criteria available from: www.health.gov.bc.ca/pharmacare/sa/criteria/formsindex.html#_Gastrointestinal_Disorders

Drug Interactions

If a clinically relevant drug interaction is suspected, it is prudent to discontinue PPI therapy in the absence of a compelling indication for PPI use.

This is not intended as an exhaustive list, but serves to summarize select clinically relevant PPI drug interactions. For complete information, please consult a drug interaction resource.

ONCOLOGY MEDICATIONS, TRANSPLANT MEDICATIONS, ANTIRETROVIRAL THERAPY[49]

- Select oncology medications, transplant medications, and antiretroviral therapy may be adversely affected by the addition of PPI therapy.
- Refer to:
  - BC Cancer Agency: www.bccancer.bc.ca/HPI/DrugDatabase/default.htm
  - BC Transplant Agency: www.transplant.bc.ca/funded_drugs.htm
  - BC Center for Excellence in HIV/AIDS: cfenet.ubc.ca/therapeutic-guidelines or Toronto General Hospital Immunodeficiency Clinic: www.hivclinic.ca/main/drugs_interact.html

OTHER MEDICATIONS (i.e., where drug-therapy modification may be recommended)[49]

- Citalopram, escitalopram (esomeprazole, omeprazole: may increase the serum concentration of these antidepressants).
- Itraconazole, systemic ketoconazole, posaconazole suspension (any PPI: may decrease the serum concentration of these azole antifungals).
- Clopidogrel:
  - It remains uncertain whether the addition of a PPI to clopidogrel therapy adversely affects cardiovascular outcomes and it is unclear if there is a difference in the risk of an interaction between specific PPIs and clopidogrel.[50-54]
  - Despite this uncertainty, the prescribing information for clopidogrel (Plavix®, generics) advises against the concurrent use of a strong or moderate cytochrome P450 2C19 inhibitor (e.g., omeprazole) because of a possible reduction in the antiplatelet activity of clopidogrel.[55] If a PPI is indicated, the clopidogrel prescribing information recommends the selection of a PPI with a lower propensity for cytochrome P450 2C19 inhibition (e.g., pantoprazole).[55-57]

4 Proton Pump Inhibitors (PPIs): Adverse Events

Observational Studies: PPI Adverse Events		
Potential Risk	**Evidence**	**Clinical Implications**
Enteric Infections *Clostridium difficile* infection (CDI), *Campylobacter*, *Salmonella*	o Systematic review (51 studies): increased risk of CDI in community and hospitalized patients, OR 1.65 (95% CI 1.47 to 1.85)[2] o Three additional systematic reviews report similar results[3-5] o Recurrent CDI risk was also increased, OR 2.51 (95% CI 1.16 to 5.44)[5] o Systematic review (4 studies): increased risk of enteric infections including *Salmonella* and *Campylobacter*, OR 3.33 (95% CI 1.84 to 6.02)[58]	o Reassess PPI indication in patients with CDI and in elderly, hospitalized patients with risk factors for enteric infections[5,40,59] o 2012 Health Canada, 2012 U.S. FDA Warning[60,61]
Fractures	o Systematic review: increased risk of hip fractures (9 studies), OR 1.25 (95% CI 1.14 to 1.37), and vertebral fractures (4 studies), OR 1.50 (95% CI 1.32 to 1.72)[6]	o Ensure a clear indication for PPI use in patients with risk factors for fracture[62] o 2011 US FDA Warning, 2013 Health Canada Warning[63,64]
Pneumonia community or hospital acquired	o Systematic review (8 studies): increased risk of pneumonia, OR 1.27 (95% CI 1.11 to 1.46)[7] o Meta-analysis (8 studies): in new users of NSAIDs prescribed PPIs the risk of hospitalization for community acquired pneumonia was not significantly increased, OR 1.05 (95% CI 0.89 to 1.25)[65]	o Conflicting evidence; should not preclude use of a PPI where there is a compelling indication[59,62]
Spontaneous Bacterial Peritonitis	o Systematic review (8 studies): increased risk of spontaneous bacterial peritonitis in hospitalized patients with cirrhosis, OR 3.15 (95% CI 2.09 to 4.74)[8]	o Ensure a clear indication for PPI use in patients with cirrhosis[8,40]
Hypomagnesemia	o Systematic review: since 2006, 36 case reports of hypomagnesemia with severe symptoms including paresthesia, seizures, and arrhythmia[66] o Case control study: patients aged ≥ 66 hospitalized with hypomagnesemia were more likely to be current users of PPIs, OR 1.43 (95% CI 1.06 to 1.93)[67]	o Consider discontinuing PPI therapy in cases of unexplained, severe hypomagnesemia[59] o 2011 U.S. FDA Warning[68]
Acute Interstitial Nephritis	o Systematic review: 60 cases of acute interstitial nephritis identified over a 15 year time frame[69]	o In PPI users with unexplained interstitial nephritis, an adverse reaction to the PPI should be considered[70]
Vitamin B12 Deficiency	o Case control study: exposure to ≥ 2 years of PPI therapy increased the risk of a new diagnosis of vitamin B12 deficiency, OR 1.65 (95% CI 1.58 to 1.73)[9]	o Screening reasonable for elderly or malnourished patients[59,62]

Notes:

- This is not an exhaustive list of all associated harms, but constitutes adverse events reported in systematic reviews or in regulatory warnings (e.g., Health Canada).
- In the Cochrane systematic reviews, reporting of PPI adverse events was incomplete with generally fewer randomized controlled trials contributing data to the safety versus the efficacy analyses.[15,16,28,32]
- Information on longer term, rare, or serious harms comes from observational studies which may not establish causation.[71]
- **When a strong indication for PPI therapy cannot be identified, clinical decision making should include consideration of possible clinically relevant harms.**[72]

OR = odds ratio (associated risk in PPI users vs. non-users); **CI** = confidence interval; **U.S. FDA** = U.S. Food and Drug Administration; **NSAIDs** = non-steroidal anti-inflammatory drugs

5 Proton Pump Inhibitors (PPIs): Reassessment and Tapering

If a PPI has been prescribed for GERD or other dyspeptic symptoms, it is reasonable to suggest titrating down to the lowest effective dose based on residual symptoms. This may include intermittent or as needed therapy rather than daily PPI therapy.[19,20,34,73]

There is no consensus on how to taper PPI therapy and it has not been rigorously studied.[74]

- Empiric tapering recommendations vary in their complexity but generally involve reducing the PPI dose over a 4 to 8 week period.
- The taper may also include a trial of discontinuing the PPI if a person is asymptomatic to assess the need for ongoing PPI therapy.[19]
- Rebound acid hypersecretion has been described after discontinuing PPI therapy, but its clinical relevance has not been well documented.[59,75]
- Maintenance PPI therapy has been recommended in select situations such as severe erosive esophagitis or Barrett's esophagus.[17,19,76,77]

Reasonable tapering recommendations include:[78,79]

- **Decreasing the PPI dose** by 50% at 1 to 2 week intervals until the PPI is discontinued or until meaningful symptoms recur.
- **Increasing the interval** between doses to every 2 to 3 days (rather than decreasing the dose) may be preferred if the lower PPI dose is more costly (see the PPI Drug Information Table for medication costs).
- Incorporating as needed histamine receptor antagonists (e.g., ranitidine) or antacids as adjunct therapies during the PPI taper.

Examples:

- Rabeprazole 20 mg once a day → reduce to rabeprazole 10 mg once a day for 2 weeks → reduce to rabeprazole 10 mg every other day for 2 weeks → discontinue PPI
- Pantoprazole 40 mg once a day → reduce to pantoprazole 40 mg every other day for 2 weeks → reduce to pantoprazole 40 mg intermittently or as needed for symptoms that interfere with quality of life

References available upon request.