PPI DEPRESCRIBING

Approaches for stopping or dose reduction of PPIs in those who may not need lifelong treatment

April 2015 (Partial Update June 2017; for drug chart, see http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-AcidSuppression.pdf)

PPI Deprescribing

PPIs are one of the most commonly prescribed medications. They are **efficacious and useful** in the management of a variety of conditions including:

- Gastroesophageal reflux disease (GERD)
- Reflux esophagitis
- *Helicobacter pylori*-associated peptic ulcer disease

{See Table 2: Proton Pump Inhibitors (PPIs): Efficacy}

PPIs are **usually well tolerated** with few short-term side effects. Some concerns have arisen regarding an association with **some long-term adverse events**. {See Table 3: PPIs: Adverse Events. } When PPIs are strongly indicated, their benefits far outweigh their theoretical risks. However, in cases where PPIs do not have a clear **ongoing** indication, it is prudent to consider deprescribing.[1]

A **PPI Deprescribing Algorithm** has been developed as part of a national Canadian project.[1] It is intended to assist clinicians in assessing the patient for current PPI indication, and guide how to deprescribe if an ongoing indication is not identified.

When stopping a PPI in someone who has been on therapy for several months, there is some concern that there may be some **symptomatic rebound acid secretion**. This could be mininterpreted as a need for ongoing therapy. It is reasonable to taper the PPI over time. {See Table 1.}

Evidence is lacking regarding an optimal tapering process. In general, **when tapering** one may either:

a) decrease the PPI dose by 50% for a few weeks or,
b) increase the interval between doses to every 2 or more days. This approach may be preferred for PPIs where a lower dose is more costly. {See Table 1}

{Antacids or an H_2 blocker such as ranitidine may be used during the taper.}

Evidence for Deprescribing of PPIs

A recent systematic review evaluated the current evidence for deprescribing of PPIs.[2] It found 6 trials (including both randomized and non-randomized) that evaluated strategies for deprescribing, all using different approaches and/or regimens. This review found:

- Successful PPI discontinuation, without deterioration in symptom control, is possible for a substantial number (14-64%) of subjects;
- The percentage who were able to totally discontinue PPIs was greater in non-GERD patients than GERD patients;
- Tapering of PPIs may be more successful than abrupt discontinuation for some subjects.

[**Update link** of interest: Tools for Practice, PPIs deprescribing; **June 26, 2017** https://www.acfp.ca/wp-content/uploads/tools-for-practice/1498232560_tfp190ppisfv.pdf]

On-Demand Versus *Intermittent* Dosing of PPIs [3,4,5,6]

***On-demand* therapy (patient-driven)**: the daily intake of medication for a period sufficient to resolve dyspepsia or GERD symptoms. Following symptom resolution, medication is discontinued until symptoms recur, at which point medication is resumed until symptoms resolve again.

***Intermittent* therapy (physician-driven)**: the daily intake of medication for a predetermined, finite period (e.g. 4 wks; range 2-8 wks). The intent is to resolve reflux-related symptoms or heal esophageal lesions following relapse of the previous symptoms or condition. It may also refer to use of a PPI on only ~3 days per week to prevent symptoms.

Both on-demand and intermittent PPI therapy are strategies to manage those with GERD not requiring lifelong daily therapy. Single PRN doses of PPIs, used only occasionally, are not generally useful for symptom control. {Single doses of an H2 blocker or an antacid may be useful.}

See also the related **patient page** on ***Stopping your PPI***.
http://www.rxfiles.ca/rxfiles/uploads/documents/Deprescribing-PPI-Patient-Tool.pdf

From ***Choosing Wisely Canada – Gastroenterology***, Oct 2014, Canadian Association of Gastroenterologists

Don't maintain long term proton pump inhibitor (PPI) therapy for gastrointestinal symptoms without an attempt to stop/reduce PPI at least once per year in most patients.

PPIs are effective drugs for the treatment of gastro-esophageal reflux disease (GERD). Patients should always be prescribed the lowest dose of drug that manages their symptoms. Even though GERD is often a chronic condition, over time the disease may not require acid suppression and it is important that patients do not take drugs that are no longer necessary. For this reason patients should try stopping their acid suppressive therapy at least once per year. Patients with Barrett's esophagus, Los Angeles Grade D esophagitis*, and gastrointestinal bleeding would be exempt from this.
Link: http://www.choosingwiselycanada.org/recommendations/gastroenterology-2/

*Note, the *PPI Deprescribing Algorithm* suggests that those with both Grade C and D esophagitis may stay on PPI therapy.

Deprescribing Medications – Some background

There is a lot of interest in the "deprescribing" of certain medications in select patients.[7,8,9] However, there are often many challenges to overcome on the way to success.

For the purposes of this newsletter, the term "deprescribing" is used to denote ***a reduction in dosage with or without discontinuation*** of the medication.

Reasons to consider deprescribing a medication

- **Changing priorities** and needs at end-of-life
- Medication **lacks a current indication**
- Medication is associated with increased risk of **potential harms** with ongoing or long-term use
- Medication associated with drug/food interactions
- Medication is of **low priority**, relative to others, and there is a desire to reduce **polypharmacy**
- Discussion reveals medication is **no longer desired or required** by the patient (shared decision making)

Three Select Medication Categories for Deprescribing

1) **PPIs:** useful in peptic ulcer disease and GERD; however, some do not require lifelong therapy that carries its own risk of harms & uncertainties.[10] It is prudent to review for current indication &/or possible PPI discontinuation, e.g. after hospital discharge.

2) **Benzodiazepines:** useful for the treatment of anxiety and short-term for insomnia; however, associated with increased risk of falls, and impaired cognition and function.[11] "Time efficient interventions" are effective in curbing long-term use in select patients.[12]

3) **Opioids in Chronic Non-Cancer Pain**: when adverse events present and/or there is no improvement in function.

Two Select Patient Groups for Deprescribing

1) **Older adults**: a variety of factors result in older adults being a prime group to assess for potential medications to deprescribe. Increased risk of medication-related adverse events, drug interactions, medication burden, shortened life expectancy, frailty and changing priorities all give reason to reassess and reduce unnecessary polypharmacy when possible.

2) **End of life / palliative care patients:** as patients near the end of life, the emphasis often shifts toward optimizing comfort and quality of life. Thus medications that have been used for primary prevention of disease may be tapered and/or discontinued. It is usually appropriate to aim for less intensive management of conditions such as *hypertension* & *diabetes*, where the *time-to-benefit* falls into a longer timeframe. Consider deprescribing:
   - ASA, statins; possibly warfarin for atrial fibrillation
   - Iron, vitamins, herbal/natural products
   - Bisphosphonates (unless used for hypercalcemia with malignancy)
   - Hormone therapy
   - Anti-hypertensives and anti-hyperglycemics

A Process for *Artful Deprescribing*

While medication reassessment and deprescribing is often a noble goal, it is equally important to have an approach that ensures positive, and not adverse, outcomes. One does not want to stop a medication that has a valid and important indication. A deprescribing trial may result in re-emergence of symptoms or a condition that was responding to the medication. Successful deprescribing should take a deliberate approach that includes:

1) Identify and prioritize potential medications.
2) Engage the patient, family and/or caregivers and make a plan. Decide whether a tapering regimen is needed and instruct on how to manage any withdrawal symptoms that may emerge.
3) Taper and/or discontinue medication and ensure adequate communication with patient, caregivers, the pharmacist, and other health professionals. {See also *Geri-RxFiles – Tapering* section.}
4) Monitor and review for any important outcomes or withdrawal symptoms.
5) Allow for discussion and shared decision making that acknowledges the patient's values & priorities.

Patient Information Tools to Assist in Deprescribing

1) **PPI Deprescribing** – see inside; also available online [13]
   1) http://www.rxfiles.ca/rxfiles/uploads/documents/Deprescribing-PPI-Patient-Tool.pdf
   2) http://www.criugm.qc.ca/fichier/pdf/PPI-EN-Men.pdf
2) **Benzodiazepine Deprescribing** – available online [14]
   http://www.criugm.qc.ca/fichier/pdf/BENZOeng.pdf
3) **Opioid Tapering Template** – available online [15]
   http://www.rxfiles.ca/rxfiles/uploads/documents/Opioid-Taper-Template.pdf

Table 1: Practical, PPI taper strategies that reduce the dose without resulting in an inadvertent increased cost

Rabeprazole PARIET	20mg daily $18	⇨ 10mg daily $15	⇨ 10mg every other day $12, or only when needed
Pantoprazole PANTOLOC	40mg daily $23	⇨ 20mg daily $21	⇨ 20mg every other day $15 {TECTA ☎▼ 40mg/d,↑'cost. $35}
Omeprazole LOSEC	20mg daily $24	⇨ 20mg every other day $16	[lower 10mg/day dose of omeprazole ↑'s cost $37]
Lansoprazole PREVACID	30mg daily $27 ☎▼	⇨ 15mg daily $27	⇨ 15mg every other day $19, or only when needed
Esomeprazole NEXIUM	40mg daily *$82 ☎ ⊗	⇨ 20mg daily $82	⇨ 20mg every other day $42, or only when needed
Dexlansoprazole DEXILANT	60mg daily *$87 ✗ ⊗	⇨ 30mg daily $87	⇨ 30mg every other day $47, or only when needed

Note: costs denote typical consumer cost per month for lowest cost generic product (SK, Canada). PPIs most effective if taken on an empty stomach ~30minutes prior to a meal. ☎=EDS in SK, ✗ =non-formulary in SK, ⊗=non-formulary NIHB. *Standard/comparative dose would be esomeprazole 20mg & dexlansoprozole 30mg per day

Table 2: **Proton Pump Inhibitors (PPIs): Efficacy ***

Systematic Reviews: Common PPI Primary Care Indications	
Evidence for Gastrointestinal Outcomes	**Clinical Implications**
Uninvestigated gastroesophageal reflux disease (GERD) [16] Heartbeat remission: PPI 72% vs. placebo 25%, **NNT 2** high QOE PPI 55% vs. H2RA 32%, **NNT 4** moderate QOE	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 [16] 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)[17,18] 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) [18,19,20,21] PPI therapy may improve symptoms in a small proportion of patients with functional (non-ulcer) dyspepsia but PPIs are not more effective than H2RAs [16] 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)[18,19,22,23,24,26] The efficacy and safety of twice daily PPI therapy is relatively unstudied for these primary care indications [25,26,27,28]
Reflux (erosive) esophagitis [29,30] **Usual Tx: 8 wks** Acute Acute healing of erosive esophagitis: PPI 83% vs. placebo 28%, **NNT 2*** PPI 80% vs. H2RA ± prokinetic 54%, **NNT 4*** Maintenance of healed esophagus: PPI 78% vs. placebo 21%, **NNT 2*** PPI 78% vs. H2RA 42%, **NNT 3*** Maintenance of symptom relief: PPI 71% vs. placebo 24%, **NNT 2*** PPI 78% vs. H2RA 56%, **NNT 4***	
Endoscopy negative reflux disease [16] † **Usual Tx: 4-8 wks** Acute Heartbeat remission: PPI 38% vs. placebo 13%, **NNT 4** moderate QOE PPI 55% vs. **H2RA** 43%, **NNT 8** low QOE	
Functional (non-ulcer) dyspepsia [31] † **Usual Tx: 2-8 wks** Acute Improvement in dyspepsia: PPI 34% vs. placebo 25%, **NNT 10*** PPI 32% vs. **H2RA** 28%, **NSS***	
Helicobacter pylori* eradication (HPE) for peptic ulcer disease** [32] Duodenal ulcer recurrence: HPE 13% vs. placebo 67%, **NNT 2 **Tx: ≤ 2wks** HPE 12% vs. maintenance ulcer healing drug 16%, **NSS*** Gastric ulcer recurrence: HPE 16% vs. placebo 50%, **NNT 3*** **Usual Tx: 4-8 wks** Acute	In *H. pylori* positive patients with peptic ulcer disease, eradication therapy decreases peptic ulcer recurrence compared to no treatment [32] 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 [18,33,34,35,36] Consult *Bugs & Drugs* for Canadian *H. pylori* recommendations [36] (App revised 2014) [RxFiles note: current variation regarding triple vs sequential vs quadruple therapy. See RxFiles 10th Ed. pg 65.]
Prevention of NSAID associated peptic ulcer [37] Endoscopic peptic ulcer: PPI 14% vs. placebo 36%, **NNT 4*** PPI vs. H2RA: insufficient direct comparative data*	The effect of PPI therapy on NSAID-associated peptic ulcer complications (e.g., bleeding, perforation, obstruction, death) has not been adequately established [37,38,39,40]
Prevention of antiplatelet associated (e.g., ASA, clopidogrel) peptic ulcer	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.[41]

% = proportion of participants with outcome; **NNT** = 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

*Table adapted/reproduced, with permission, from BC PAD Service, 29 Jan 2015. †denotes therapeutic areas where there is minimal difference in efficacy between H2RAs & PPIs.

Table 3: **Proton Pump Inhibitors (PPIs): Adverse Events** *

Observational Studies: PPI Adverse Events		
Potential Risk	**Evidence**	**Clinical Implications**
Enteric Infections *Clostridium difficile* infection (CDI), *Campylobacter*, *Salmonella*	Systematic review (51 studies): increased risk of CDI in community and hospitalized patients, OR 1.65 (95% CI 1.47 to 1.85) [42] Three additional systematic reviews report similar results [43,44,45] Recurrent CDI risk was also increased, OR 2.51 (95% CI 1.16 to 5.44) [41] Systematic review (4 studies): increased risk of enteric infections including *Salmonella* and *Campylobacter*, OR 3.33 (95% CI 1.84 to 6.02) [46]	Reassess PPI indication in patients with CDI and in elderly, hospitalized patients with risk factors for enteric infections [36,45,47] 2012 Health Canada, 2012 U.S. FDA Warning [48,49]
Fractures	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)[50]	Ensure a clear indication for PPI use in patients with risk factors for fracture [51] 2011 US FDA Warning, 2013 Health Canada Warning [52,53]
Pneumonia community or hospital acquired	Systematic review (8 studies): increased risk of pneumonia, OR 1.27 (95% CI 1.11 to 1.46) [54] 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) [55]	Conflicting evidence; should not preclude use of a PPI where there is a compelling indication[51,56] 2016 Observational study, suggests association, not causation. [68]
Spontaneous Bacterial Peritonitis	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) [57]	Ensure a clear indication for PPI use in patients with cirrhosis [36,57]
Hypomagnesemia	Systematic review: since 2006, 36 case reports of hypomagnesemia with severe symptoms including paresthesia, seizures, and arrhythmia [58] 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) [59]	Consider discontinuing PPI therapy in cases of unexplained, severe hypomagnesemia [56] 2011 U.S. FDA Warning [60]
Acute Interstitial Nephritis / CKD	Systematic review: 60 cases of acute interstitial nephritis identified over a 15 year time frame [61] {Update [Jan16]. Observational 14 year trial suggests ↑CKD risk for PPI users, unadjusted HR = 1.45 [95% CI, 1.11-1.90]; risk persisted for all analysis. [66]}	In PPI users with unexplained interstitial nephritis, an adverse reaction to the PPI should be considered [62] Ensure a clear indication for long-term PPI use.
Vitamin B12 Deficiency	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) [63]	Screening reasonable for elderly or malnourished patients [47,52]

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 Cochrane systematic reviews, reporting of PPI adverse events was incomplete with generally fewer RCTs contributing data to the safety versus the efficacy analyses. [16,29,30,31]

Information on longer term, rare, or serious harms come from observational studies which may not establish causation. [64]

{Update [Feb16]. Observational data raises question about a possible link between regular PPI use and risk of dementia [67] & pneumonia [68]}

When a strong indication for PPI therapy cannot be identified, clinical decision making should include consideration of possible clinically relevant harms. [65]

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

*Table reproduced from BC PAD Service, 29 Jan 2015. Used with permission.

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