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THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

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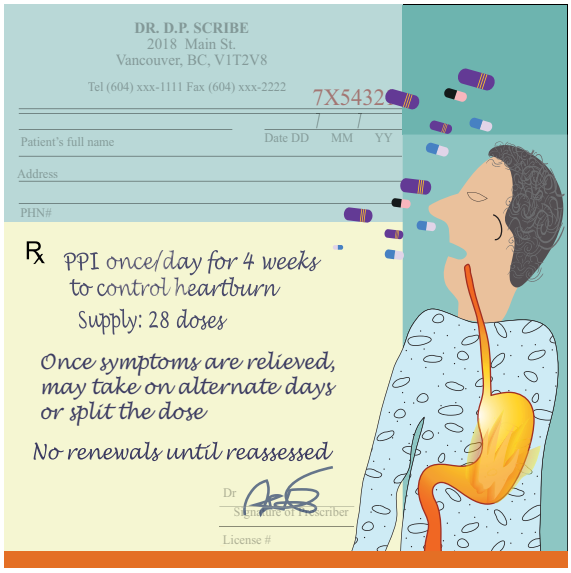
Deprescribing Proton Pump Inhibitors



The first PPI was approved in Canada in 1988. Pronounced and durable reduction of stomach acid production made omeprazole a "blockbuster drug", spawning multiple imitators. Eventually this included (as patent extensions) the single enantiomers esomeprazole and dexlansoprazole. Prescription PPIs are approved for peptic ulcer disease (PUD), gastro-esophageal reflux (GERD), and non-ulcer dyspepsia. About 1 in 12 British Columbians receives a prescription in any year.[1] Over the counter omeprazole and esomeprazole are also approved for heartburn occurring on >2 days/week, achieving full acid suppressant effect in 1-4 days.[2] Most people taking PPIs have not been endoscoped, so that "GERD" often refers to reflux or heartburn.

Our previous reviews[3-9] of randomized clinical trial (RCT) evidence on PPIs concluded:

- Over 8-12 weeks, PPIs are effective for GERD[3] and PUD[4].
- Patients treated effectively do not require chronic acid suppressive medications.[4]
- Long-term PPIs are appropriate in relapsing severe erosive esophagitis.[3]
- No PPI demonstrated superiority for GERD or symptoms related to PUD.[9]
- No long-term RCTs monitored adverse effects of PPIs.[9]

Understanding serious long-term adverse effects of PPIs thus relies on observational studies showing that PPIs are associated with an increased risk of a variety of serious adverse events. These include enteric infections (notably *C. difficile*), spontaneous bacterial peritonitis, fractures, hypomagnesemia, acute interstitial nephritis, iron deficiency, vitamin B_{12} deficiency, gastric polyps and gastric cancer.[8] Recently, dementia was added to this list.[10] The apparent association with serious pneumonia may not be causative.[11] Yet strong acidity in the stomach has long evolutionary roots, and acid may function as an "ecological filter" against harmful ingested microbes.[12]

An obligation to consider deprescribing?

Studies in the US, Australia, and UK found that 40-65% of hospitalized people taking long-term PPIs, and 40-55% of primary care outpatients, had no documented reason for taking a PPI.[13] In BC, 34% of people in residential care did not have a documented indication for their PPI prescription.[14]

Without evidence of long-term effectiveness, costs and harms create a clinical obligation to consider deprescribing PPIs in many people taking long-term therapy.

A Cochrane review of evidence for PPI deprescribing found six RCTs lasting 6-months (N=1758). Five RCTs compared continued PPI use with on-demand use; one compared continued use with abrupt cessation.[15] Unlike the majority of patients who take PPI for mild symptoms or unknown indications, most trial participants had moderately severe reflux esophagitis, for whom deprescribing is less likely to be effective. The trials were small, short in duration, and did not record clinical outcomes most relevant to benefits or harms of deprescribing. Thus, there are no RCT data to inform conclusions about long-term benefits or harms of PPI continuation, reduction, or discontinuation.

Guideline for deprescribing PPIs

A non-industry funded Canadian Deprescribing Network guideline is now available.[13] The authors searched for evidence to help clinicians decide when and how to safely taper or stop PPI, using Cochrane methodology and the GRADE framework for guideline development. They define deprescribing of PPIs as:

- dose reduction;
- change to intermittent or on demand use;
- substituting a histamine 2 receptor antagonist (H2RA); or
- complete cessation of PPI.

Having found no evidence comparing these approaches, the Canadian guideline recommends deprescribing PPIs in adults who have completed a minimum of 4 weeks of PPI treatment and whose

Mailing Address: Therapeutics Initiative
The University of British Columbia
Department of Anesthesiology, Pharmacology & Therapeutics
2176 Health Sciences Mall
Vancouver, BC Canada V6T 1Z3

Tel.: 604 822 0700
Fax: 604 822 0701
E-mail: info@ti.ubc.ca
www.ti.ubc.ca

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upper GI symptoms are resolved. This recommendation does not apply to people with Barrett esophagus, severe esophagitis, or a documented history of bleeding ulcers. The authors suggest on-demand use or a clinically reasonable tapering schedule:

- Reduce PPI dose by half at 1-2-week intervals until the PPI is discontinued; or
- Increase dosing interval from daily to every 2-3 days.

Switching to H2RA or oral antacids during the taper may also be helpful.

The guideline discusses how to monitor patients. In deprescribing experiments, patients were followed at 4 and 12 weeks after stopping a PPI, and again at 6-12 months. Differentiating "rebound hypersecretion" from non-acid symptoms of gastroesophageal reflux is challenging.

Efficacy of on-demand PPI use

AstraZeneca (discoverer of omeprazole) sponsored research showing by 1999 that on-demand use of 10 or 20 mg was more effective than placebo for preventing recurrence of heartburn in 424 patients without demonstrated esophagitis.[16] The more potent enantiomer esomeprazole acted similarly in 342 patients randomized to 20 mg vs. placebo on-demand.[17] The active group used esomeprazole on about 1 in 3 days, leading to the novel conclusion that on-demand therapy "provides a more individualized approach to management of the patient with GERD, whereby the patient dictates the extent of drug usage according to his or her specific needs." Repeating similar studies led a recent report to emphasize that on-demand PPIs for non-life-threatening conditions have "obvious potential benefits in terms of cost of treatment and convenience to patients."[18] This is partly because inhibition of acid secretion lasts much longer than the elimination half-life of PPIs.

Dose splitting is an inexpensive way to reduce daily dosage. Product monographs advise against this, because PPIs are subject to gastric acid degradation before reaching their absorptive site in the small bowel. However, "chasing" a dose with water to help empty the stomach ensures absorption of dissolved omeprazole and esomeprazole.[19] For non-life-threatening conditions, dose splitting is thus a pharmacologically reasonable option.

The Canadian Association of Gastroenterology (CAG) and Choosing Wisely Canada support deprescribing, recommending that **"PPI therapy for gastrointestinal symptoms should not be maintained long term without an attempt to stop/reduce them at least once per year in most patients."**[20]

Conclusions

- **Many patients take PPIs well beyond the recommended course of treatment. This incurs inconvenience, costs and potential for harms.**
- **Do not prescribe or renew PPIs without a well-documented indication and therapeutic goal. Write the indication and duration of therapy in the directions, to ensure this appears on the prescription label.**
- **Consider deprescribing PPIs after 4 weeks of treatment when symptoms have resolved. Start with reduced dose or a longer interval, switching to on-demand dosing or discontinuation when successful.**
- Patients capable of "chasing" a dose with water to facilitate stomach emptying can consider dose-splitting to save money.
- Informed patient consent and a strategy to deal with recurrent symptoms enhance success. For more information, consult the high-quality resources shown below.

PPI DEPRESCRIBING RESOURCES:

- **www.deprescribing.org**
- PPI Evidence-Based Deprescribing Guideline
- RXFiles (Saskatchewan) on Deprescribing PPIs
- BC Provincial Academic Detailing Service: Proton Pump Inhibitors in Primary Care
- Alberta College of Family Physicians: Tools for Practice. PPIs: Is Perpetual Prescribing Inevitable?

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For a complete list of references and links to PPI deprescribing resources go to: **www.ti.ubc.ca/letter111**

The draft of this Therapeutics Letter was submitted for review to 130 experts and primary care physicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.

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