Deprescribing proton pump inhibitors

Evidence-based clinical practice guideline

Barbara Farrell PharmD ACPR FCSHP **Kevin Pottie** MD CCFP MCISc FCFP **Wade Thompson** **Taline Boghossian** ACPR **Lisa Pizzola** MSc **Farah Joy Rashid** ACPR **Carlos Rojas-Fernandez** PharmD **Kate Walsh** ACPR **Vivian Welch** PhD **Paul Moayyedi** MB ChB PhD MPH

Abstract

Objective To develop an evidence-based guideline to help clinicians make decisions about when and how to safely taper or stop proton pump inhibitors (PPIs); to focus on the highest level of evidence available and seek input from primary care professionals in the guideline development, review, and endorsement processes.

Methods Five health professionals (1 family physician, 3 pharmacists, and 1 gastroenterologist) and 5 nonvoting members comprised the overall team; members disclosed conflicts of interest. The guideline process included the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach, with a detailed evidence review in in-person, telephone, and online meetings. Uniquely, the guideline development process included a systematic review of PPI deprescribing trials and examination of reviews of the harm of continued PPI use. Narrative syntheses of patient preferences and resource-implication literature informed recommendations. The team refined guideline content and recommendation wording through consensus and synthesized clinical considerations to address common front-line clinician questions. The draft guideline was distributed to clinicians and then to health care professional associations for review and revisions made at each stage. A decision-support algorithm was developed in conjunction with the guideline.

Recommendations This guideline recommends deprescribing PPIs (reducing dose, stopping, or using "on-demand" dosing) in adults who have completed a minimum of 4 weeks of PPI treatment for heartburn or mild to moderate gastroesophageal reflux disease or esophagitis, and whose symptoms are resolved. The recommendations do not apply to those who have or have had Barrett esophagus, severe esophagitis grade C or D, or documented history of bleeding gastrointestinal ulcers.

Conclusion This guideline provides practical recommendations for making decisions about when and how to reduce the dose of or stop PPIs. Recommendations are meant to assist with, not dictate, decision making in conjunction with patients.

EDITOR'S KEY POINTS

- Many patients continue to take proton pump inhibitors (PPIs) beyond the recommended course of treatment, and this has potential for harm and large economic implications.
- Systematic review of the evidence for PPI deprescribing (reducing dose, discontinuing, switching to "on-demand" dosing) failed to demonstrate important clinical harms in deprescribing PPIs in adults.
- This guideline recommends deprescribing PPIs in adults who have completed a minimum 4-week course of PPI treatment, resulting in resolution of upper gastrointestinal symptoms.
- Future PPI deprescribing research should address deprescribing for other PPI indications and in the frail elderly population, optimal tapering regimens or alternate treatments to minimize symptom recurrence, consistent approaches to measuring outcomes, measurement of both positive and adverse drug withdrawal events, long-term harms and benefits, and costs.

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Deprescribing is the planned and supervised process of dose reduction or stopping of medication that might be causing harm or might no longer be providing benefit.[1] The goal of deprescribing is to reduce medication burden and harm while maintaining or improving quality of life. However, deprescribing can be difficult, especially when medications do not appear to be causing overt harm.[2] In an effort to provide evidence-based recommendations and tools to aid clinicians in stopping medications that

might no longer be needed or that might be causing harm, we initiated the Deprescribing Guidelines in the Elderly project **(www.open-pharmacy-research.ca/research-projects/emerging-services/deprescribing-guidelines)**.

Proton pump inhibitors (PPIs) were selected in a national modified Delphi consensus process as an important medication class for developing deprescribing guidelines, given their high prevalence of use and overuse.[3]

Concern about overuse of PPIs has been growing.[4-6] In a report summarizing prescription drug use in Canada, pantoprazole was the fifth most common drug prescribed, with more than 11 million prescriptions dispensed in 2012.[7] Most common indications such as gastroesophageal reflux disease (GERD) require short-term treatment (ie, up to 4 to 8 weeks).[8-10] However, chronic use appears to be problematic, with studies showing a lack of documented ongoing indication for between 40% and 65% of hospitalized patients in the United States and Australia[11-13] and between 40% and 55% of primary care patients in the United States and the United Kingdom.[4,14]

Proton pump inhibitors are often viewed as safe and well tolerated medications, and while the incidence of side effects, such as diarrhea,[15] impaired B12 absorption,[16] hypomagnesemia,[12,17] *Clostridium difficile* infection,[18] hip fractures,[19] and pneumonia[20] might be small, older people might be at higher risk of these conditions.[21] When PPIs are inappropriately prescribed or used for too long, they can contribute to polypharmacy with its attendant risks of nonadherence, prescribing cascades, adverse reactions, medication errors, drug interactions, emergency department visits, and hospitalizations.[22-24] In addition, there are economic implications of overuse of PPIs. Spending on PPIs by public drug programs in Canada (excluding Quebec and the territories) totaled $249.6 million of the $7.8 billion spent on prescription drugs by these programs in 2013.[25]

Our target audience includes primary care physicians, pharmacists, nurse practitioners, and specialists who care for patients who might use PPIs.

The target population includes adults older than 18 years of age (including the elderly) taking a continuous PPI for longer than 28 days for the purpose of treating GERD or esophagitis. The guideline does not apply to those with Barrett esophagus, those with severe esophagitis (grade C or D on endoscopy, as outlined in **Box 1**),[26] or those with documented history of bleeding gastrointestinal (GI) ulcers. Individual situations in which there might be risk factors that warrant continued use of PPIs are also outlined.

METHODS

We used a comprehensive checklist for a successful guideline enterprise to develop the methods for the PPI deprescribing guideline.[27,28]

Box 1. Los Angeles Classification for the endoscopic assessment of reflux esophagitis

The classification uses a 4-grade system

- Grade A: 1 or more mucosal breaks no longer than 5 mm, none of which extends between the tops of the mucosal folds
- Grade B: 1 or more mucosal breaks more than 5 mm long, none of which extends between the tops of 2 mucosal folds
- Grade C: Mucosal breaks that extend between the tops of 2 or more mucosal folds but that involve less than 75% of the esophageal circumference
- Grade D: Mucosal breaks that involve at least 75% of the esophageal circumference

Data from Saraf et al.[26]

The Guideline Development Team (GDT) comprised 5 clinicians—a family physician (K.P.), a gastroenterologist (P.M.), and 3 pharmacists (B.F., C.R.F., K.W.)—and 5 nonvoting members—a methodologist (V.W.), 2 pharmacy residents (F.J.R., T.B.), and 2 project coordinators (W.T., L.P.). Additional support was provided by a librarian and a master's student. Three GDT members were investigators with the Deprescribing Guidelines in the Elderly project (B.F., K.P., C.R.F.). All GDT members had expertise in the clinical management of patients taking PPIs. Team members' expertise, role descriptions, and conflict of interest statements are available at **CFPlus**.*

We used the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system for guideline development (**Box 2**).[29-32] The GDT articulated the main clinical management question as follows, using the PICO (patient or problem, intervention, comparison, outcome) approach: In adults, what are the effects (harms and benefits) associated with deprescribing long-term daily PPI therapy compared with continuous and chronic use? Definitions specific to PPI deprescribing were articulated by the GDT and are listed in **Box 3**.[6,33]

To ensure studies of all deprescribing approaches for PPI were captured, 2 search strategies were used. We conducted a de novo systematic review to assess effects of on-demand and abrupt-discontinuation deprescribing for people using PPIs for longer than 4 weeks.[30,31] The methodology and the search strategy used to conduct this systematic review are outlined in a published protocol.[30] Next, we updated a previously published Cochrane systematic review on dose lowering and stepping down

*Descriptions of contributors' **expertise, roles, and conflicts of interest;** the **GRADE evidence tables**; frequency ratios for the harms associated with proton pump inhibitor use; **evidence reviews**; a **patient handout**; and an easy-to-print version of the **algorithm** are available at **www.cfp.ca**. Go to the full text of the article online and click on the **CFPlus** tab.

Box 2. Notes on the GRADE framework for guideline development

This guideline was developed in accordance with the methods proposed by the GRADE Working Group[29] and was informed by a systematic review[30,31] and a subset of data from an existing systematic review[32]

- We focused our review and recommendations on outcomes important to patients, such as harms or benefits resulting from deprescribing a PPI, pill burden, and cost or resource use. Outcomes were proposed by the systematic review team and revised by the Guideline Development Team based on feasibility and the literature available
- Ratings of the evidence profile tables included high, moderate, low, or very low and depended on our confidence in estimates of effect. Because only randomized controlled trials were used, they started with a high quality rating, but could be rated down by limitations in any of 4 domains: risk of bias, inconsistency, indirectness, and imprecision. Publication bias could not be rated owing to the paucity of studies.[29] Other areas that were considered in formulating a final rating included harms, patient values and preferences, and resource use
- The GRADE Working Group outlines appropriate wording for recommendations depending on the rating of strength and confidence in the evidence. A strong recommendation with implications for patients (phrased as "we recommend ...") implies that all patients in the given situation would want the recommended course of action, and only a small proportion would not. A weak recommendation (phrased as "we suggest ...") implies that most patients would wish to follow the recommendation, but some patients would not. Clinicians must help patients make management decisions consistent with the patients' values and preferences. Implications for clinicians are similar such that a strong recommendation implies all or most patients should receive the intervention. A weak recommendation should prompt a clinician to recognize that different choices will be appropriate for individual patients

GRADE—Grading of Recommendations Assessment, Development and Evaluation; PPI—proton pump inhibitor.

to histamine-2 receptor antagonist (H_2RA) therapy.[32] Summarized pooled estimates of treatment effects from both systematic reviews for important and critical outcomes for decision making are provided in GRADE evidence tables, available at **CFPlus**.*

The systematic reviews focused on outcomes relevant to patients, caregivers, and health care providers. Primary outcomes included change in upper GI symptoms (positive or negative), pill burden, and cost. Secondary outcomes included patient satisfaction, positive drug withdrawal events (eg, resolution of a side effect such as diarrhea), and adverse drug withdrawal events (eg, recurrence of esophagitis on endoscopy).

Box 3. Definitions of PPI deprescribing

Deprescribing can include stopping, stepping down, or reducing doses

- Stopping can be done either via abrupt discontinuation or a tapering regimen
- Stepping down involves abrupt discontinuation or tapering of the PPI followed by prescription of an H_2RA (any H_2RA at any approved dose and dosing interval according to the drug monograph)
- Reducing includes the following subcategories:
  - -Intermittent PPI use, which is defined by the Canadian Consensus Conference as "daily intake of a medication for a predetermined, finite period (usually two to eight weeks) to produce resolution of reflux-related symptoms or healing of esophageal lesions following relapse of the individual's condition"[33]
  - -On-demand PPI use, which is defined by the Canadian Consensus Conference as "the daily intake of a medication for a period sufficient to achieve resolution of the individual's reflux-related symptoms; following symptom resolution, the medication is discontinued until the individual's symptoms recur, at which point, medication is again taken daily until the symptoms resolve"[33]
  - -Lower dose, which is a reduction from a standard dose to a maintenance dose[6]

H_2RA—histamine-2 receptor antagonist, PPI—proton pump inhibitor.

Draft recommendations were initially formulated by the GDT members (during an in-person meeting) from the evidence tables using confidence in estimated effects (following dose lowering, switching to on-demand therapy, or stepping down to H_2RA therapy), and taking into account literature on patient preferences for PPI use, a review of harms of continuing PPIs, team members' clinical experience with such harms, and resource implications (both in terms of PPI costs and costs that might be associated with complications arising from stopping PPIs). The GDT members met by teleconference to review and discuss recommendations drafted from the in-person meeting. Voting on the recommendations was subsequently conducted anonymously by e-mail. Unanimous agreement was sought; 80% agreement among the 5 GDT members was considered the cutoff for consensus. All 5 members of the PPI deprescribing GDT agreed with the final recommendations.

RECOMMENDATIONS

The recommendations are outlined in **Box 4**. The algorithm developed for this guideline is provided in **Figure 1**. The rationale for the recommendations is outlined in **Table 1**. The recommendations apply to adults

Box 4. Recommendations

For adults (>18 y) with upper GI symptoms, who have completed a minimum 4-wk course of PPI treatment, resulting in resolution of upper GI symptoms, we recommend the following:

- Decrease the daily dose or stop and change to on-demand (as needed) use (strong recommendation, low-quality evidence)

Alternatively, we suggest the following:

- Consider an H_2RA as an alternative to PPIs (weak recommendation, moderate-quality evidence)

GI—gastrointestinal, H_2RA—histamine-2 receptor antagonist, PPI—proton pump inhibitor.

who have completed a minimum 4-week course of PPIs for upper GI symptoms. The evidence base mainly relates to patients with GERD or esophagitis but can be extrapolated to other upper GI disorders for which the efficacy of PPIs is more modest or for which short-term use is usually recommended (eg, stress ulcer prophylaxis, peptic ulcer disease) and therefore deprescribing is likely to be more effective.[34] The recommendations do not apply to those who have or have had Barrett esophagus, severe esophagitis grade C or D, or documented history of bleeding GI ulcers.

For those with mild to moderate GERD or upper GI symptoms who have no ongoing symptoms, lowering the dose of a PPI does not lead to significantly greater relapse compared with continuing at a standard dose. Lowering the PPI dose was believed to have greater benefit than harm owing to a lack of evidence of harm, the potential to reduce costs, and the potential to reduce the risk of rare PPI side effects and drug interactions. Both on-demand therapy and stepping down to H_2RA therapy increase the risk of symptom relapse more so than lowering the dose does. However, on-demand use is associated with lower pill burden and cost, which might be desirable to patients. Please refer to **Box 2**[29-32] for definitions of the strength and quality of deprescribing trial evidence and to **Table 1** for evidence to recommendations considerations across all decision domains (quality of evidence, balance of benefits and harms, patient values and preferences, and resource implications).

Based on a lack of evidence of serious harm from deprescribing, the evidence for the benefits of reducing inappropriate PPI use in terms of pill burden and reduced risk of side effects, the high societal cost of inappropriate PPI use, and the feasibility of a PPI deprescribing intervention, we rated the recommendation to lower the dose or switch to on-demand PPI use as *strong*. The recommendation to step down to H_2RA therapy was rated as *weak* owing to the higher risk of symptom return.

Consideration of harm includes the potential for commonly reported side effects such as diarrhea, headache, and vitamin B12 and magnesium deficiency, as well as associations with increased risk of fractures, *C difficile* infection, community-acquired pneumonia, gastric cancer, gastric atrophy, intestinal metaplasia, colorectal cancer, bacterial peritonitis, small intestine bacterial overgrowth, and possibly increased vascular events in those taking clopidogrel. (Frequency ratios of the harms are available at **CFPlus**.*)

With regard to patient values and preferences, PPIs are considered to improve quality of life, but patients often do not take them daily as prescribed; some patients taking on-demand PPIs are more willing to continue treatment. Some fear recurrence of symptoms, and for this reason the guideline contains clinical considerations for alternative management strategies for occasional symptoms. (The evidence reviews and related references are available at **CFPlus**.*)

Spending on PPIs is high ($249.6 million for public drug programs across Canada [except Quebec and the territories] in 2013).[25] Studies consistently show inappropriate PPI use in 40% to 65% of patients,[4,11-14] suggesting considerable health care dollars are spent on therapy that might not be providing benefit. Step-down, intermittent, and on-demand PPI use reduces direct medical costs; however, there is no evidence comparing these strategies. The cost-effectiveness of continuous treatment for those with severe GERD has been demonstrated, and for this reason, patients with severe GERD should continue PPI treatment at the lowest effective dose. (The evidence reviews and related references are available at **CFPlus**.*)

Clinical considerations

This guideline is a tool to be used together with consideration of a patient's personal and medical context. Patients might be less accustomed to dialogue about reducing or stopping medications, and so heightened health care provider awareness to potential concerns might help foster improved patient uptake. The decision to continue, reduce, or discontinue a medication is based on a balance of knowledge about its indication and effectiveness, and risks of use including actual or potential side effects, drug interactions, pill burden, and cost. Patient and family values and preferences play an important role. Decisions about continuing, tapering, or stopping medications should be consistent with the patient's goals of care. We developed a patient pamphlet to facilitate discussion, which is available at **CFPlus**.*

The following questions were articulated by the GDT as being important to consider when making decisions about the steps for deprescribing PPIs.

Figure 1 | Proton Pump Inhibitor (PPI) Deprescribing Algorithm

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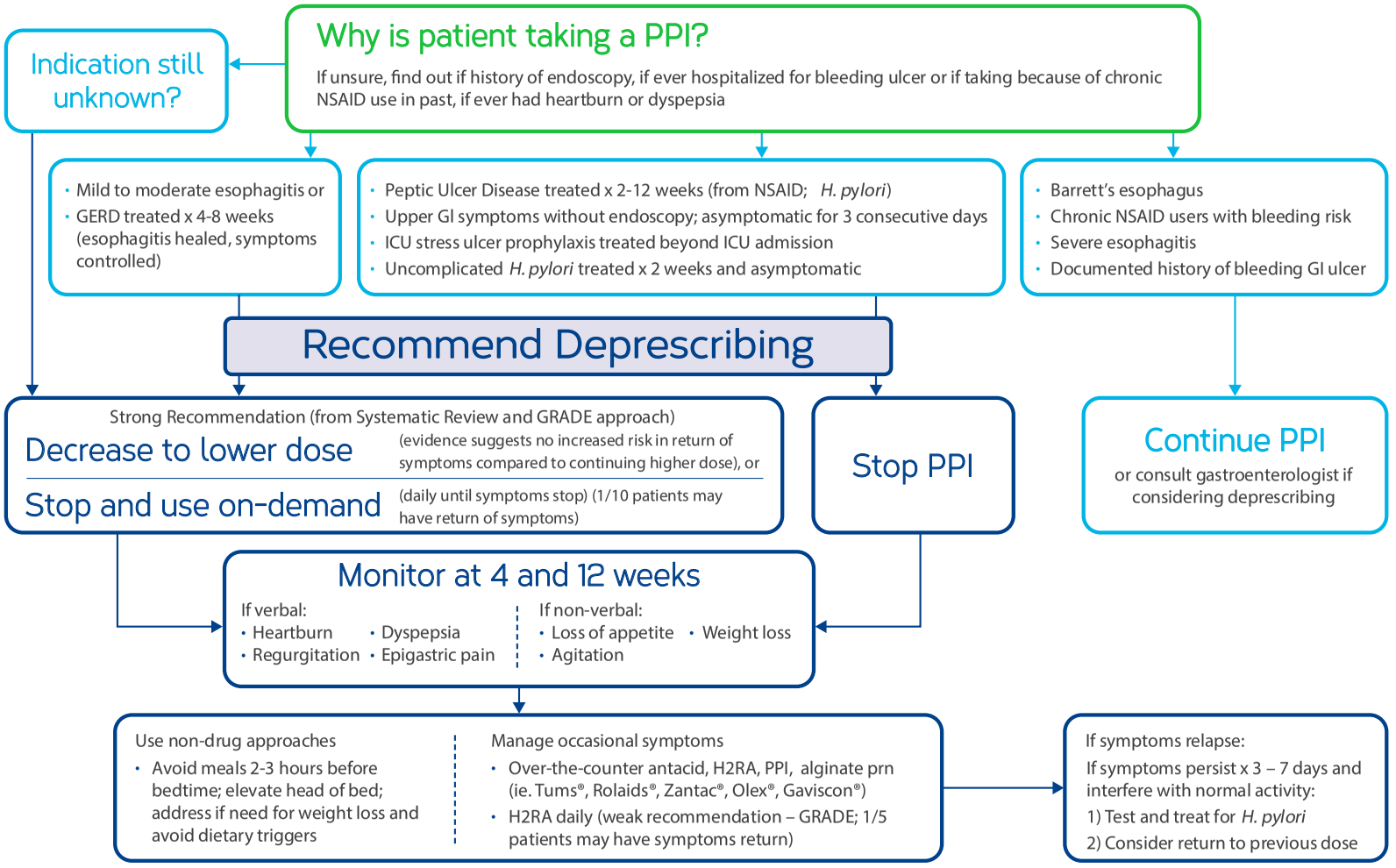

Farrell B, Pottie K, Thompson W, Boghossian T, Pizzola L, Rashid FJ, et al. Deprescribing proton pump inhibitors. Evidence-based clinical practice guideline. *Can Fam Physician* 2017;63:354-64 (Eng), e253-65 (Fr).

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deprescribing.org | Proton Pump Inhibitor (PPI) Deprescribing Notes

PPI Availability

PPI	Standard dose (healing) (once daily)*	Low dose (maintenance) (once daily)
Omeprazole (Losec®) - Capsule	20 mg+	10 mg+
Esomeprazole (Nexium®) - Tablet	20[a] or 40[b] mg	20 mg
Lansoprazole (Prevacid®) - Capsule	30 mg+	15 mg+
Dexlansoprazole (Dexilant®) - Tablet	30[c] or 60[d] mg	30 mg
Pantoprazole (Tecta®, Pantoloc®) - Tablet	40 mg	20 mg
Rabeprazole (Pariet®) - Tablet	20 mg	10 mg

Legend

a Non-erosive reflux disease

b Reflux esophagitis

c Symptomatic non-erosive gastroesophageal reflux disease

d Healing of erosive esophagitis

+ Can be sprinkled on food

* Standard dose PPI taken BID only indicated in treatment of peptic ulcer caused by *H. pylori*; PPI should generally be stopped once eradication therapy is complete unless risk factors warrant continuing PPI (see guideline for details)

Key

GERD = gastroesophageal reflux disease

NSAID = nonsteroidal anti-inflammatory drugs

H2RA = H2 receptor antagonist

SR = systematic review

GRADE = Grading of Recommendations Assessment, Development and Evaluation

Engaging patients and caregivers

Patients and/or caregivers may be more likely to engage if they understand the rationale for deprescribing (risks of continued PPI use; long-term therapy may not be necessary), and the deprescribing process

PPI side effects

- When an ongoing indication is unclear, the risk of side effects may outweigh the chance of benefit
- PPIs are associated with higher risk of fractures, *C. difficile* infections and diarrhea, community-acquired pneumonia, vitamin B12 deficiency and hypomagnesemia
- Common side effects include headache, nausea, diarrhea and rash

Tapering doses

- No evidence that one tapering approach is better than another
- Lowering the PPI dose (for example, from twice daily to once daily, or halving the dose, or taking every second day) OR stopping the PPI and using it on-demand are equally recommended strong options
- Choose what is most convenient and acceptable to the patient

On-demand definition

Daily intake of a PPI for a period sufficient to achieve resolution of the individual's reflux-related symptoms; following symptom resolution, the medication is discontinued until the individual's symptoms recur, at which point, medication is again taken daily until the symptoms resolve

Farrell B, Pottie K, Thompson W, Boghossian T, Pizzola L, Rashid FJ, et al. Deprescribing proton pump inhibitors. Evidence-based clinical practice guideline. *Can Fam Physician* 2017;63:354-64 (Eng), e253-65 (Fr).

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Table 1. Evidence to recommendations table: *Does deprescribing PPIs (dose reduction, on-demand use, abrupt discontinuation, stepping down to H_2RA therapy) compared with continuous PPI use result in benefits or harms for adults > 18 y (excluding those with history of bleeding ulcer, Barrett esophagus, and severe esophagitis grade C and D) in primary care and long-term care settings?*

DECISION DOMAIN	SUMMARY OF REASON FOR DECISION	SUBDOMAINS INFLUENCING DECISION
QoE: Is there high- or moderate-quality evidence Yes ☐ No ☑ (See references 1-16 in the evidence reviews at **CFPlus***)	The QoE for symptom relapse with deprescribing is low • Low-dose PPIs did not lead to significantly greater relapses than standard-dose PPIs did (RR = 1.16, 95% CI 0.93 to 1.44); on-demand PPI use and step down to an H_2RA increased risk of symptom relapse compared with continuous PPI use (RR = 1.71, 95% CI 1.31 to 2.23, and RR = 1.92, 95% CI 1.44 to 2.58, respectively)	*QoE for benefits with on-demand use:* moderate • Lower pill burden: 3.5 fewer pills per week (95% CI -4.89 to -2.18)
Balance of benefits and harms: Is there certainty that the benefits outweigh the harms? Yes ☑ No ☐ (See the description of harms and references 17-20 in the evidence reviews at **CFPlus***)	Our systematic review showed that low-dose PPIs did not lead to a significantly higher GI relapse rate compared with standard doses. On-demand PPI use reduced pill burden. Cost, rare PPI side effects, and drug interactions were noted as potential concerns for continuous PPI use. Low-dose PPIs were thus considered to clearly have greater benefits than harms. On-demand PPI use and a step-down approach to H_2RAs were also noted to have benefits over harms, but this was not as certain as the other deprescribing approach	Is the baseline risk for benefit similar across subgroups? Yes ☑ No ☐ • No evidence that benefits are different in subgroups Should there be separate recommendations for subgroups based on risk levels? Yes ☐ No ☑ • No evidence of benefit for any risk level Is the baseline risk for harm similar across subgroups? Yes ☑ No ☐ • No evidence that harms would be different for subgroups Should there be separate recommendations for subgroups based on harms? Yes ☐ No ☑ • No evidence for harms in subgroups
Values and preferences: Is there confidence in the estimate of relative importance of outcomes and patient preferences? Yes ☐ No ☑ (See references 1-3 and 21-25 in the evidence reviews at **CFPlus***)	In semistructured interviews patients reported that they believed PPIs were effective for preventing GI symptoms. However, it was also noted that most patients with GERD do not take their PPIs on a regular basis, and this has led to on-demand PPI research. Dose-lowering studies did not report patient satisfaction, while on-demand studies did not provide clear evidence on patient satisfaction	*Perspective taken:* the guideline group put high value on the lack of evidence of serious harms of deprescribing and on the reduction of medications and related harms and medication costs. Less value was placed on lack of information to determine the variability of patient values and preferences on different deprescribing approaches *Source of values and preferences:* semistructured interviews and other qualitative studies *Source of variability, if any:* variability difficult to estimate Method for determining values satisfactory for this recommendation? Yes ☑ No ☐ • Clear preference to use PPIs to prevent GERD, but also evidence for on-demand and other reduced-dose use All critical outcomes measured? Yes ☑ No ☐ • More information on the various describing approaches would be helpful, but available evidence was clear
Resource implications: Are the resources worth the expected net benefit? Yes ☑ No ☐ (See references 19 and 26-39 in the evidence reviews at **CFPlus***)	In Canada, PPI use accounts for a high proportion of public drug program spending ($249.6 million in 2013). The recommended treatment duration for GERD, the most common GI symptom, is 4 wk; thus much of this PPI use is inappropriate. Several studies have demonstrated interventions to reduce PPIs are feasible. On-demand trials led to reduced pill burden. The cost of stopping PPIs, however, should be balanced against possible increased visits to physicians. Cost-effectiveness analyses were not available	*Feasibility:* Is this intervention generally available? Yes ☑ No ☐ *Opportunity cost:* Is this intervention and its effects worth withdrawing or not allocating resources from other interventions? Yes ☑ No ☐ • The budget for PPIs is $69 million, and inappropriate PPI use is a considerable problem in adults and the elderly Is there a lot of variability in resource requirements across settings? Yes ☐ No ☑ • Deprescribing guidelines and implementation were considered to have relatively low resource requirements and to be feasible in primary care and long-term care
Strength of main recommendation: strong	Based on the lack of evidence of harm, the evidence for benefits of reducing inappropriate PPI use, the societal cost of inappropriate PPI use, and the feasibility of this intervention in primary care and long-term care	
Remarks and values and preference statement	The strong recommendation refers to low-dose or on-demand (as needed) PPI use. The weak recommendation refers to stepping down to H_2RA therapy as a deprescribing approach. These recommendations place high value on zero to minimal clinical risk of deprescribing and on the inappropriate use of PPIs and resources, given the high cost associated with long-term PPI use, and some value on the potential harms and remote side effects (eg, pneumonia, diarrhea, *Clostridium difficile*, osteoporosis)	

GERD—gastroesophageal reflux disease, GI—gastrointestinal, H_2RA—histamine-2 receptor antagonist, PPI—proton pump inhibitor, QoE—quality of evidence, RR—relative risk.

Are there indications or risk factors that warrant continued use? An important first step is determining the original indication for the PPI and whether there are ongoing risk factors for GI disease that warrant chronic use. Reviewing patient history and consultation notes for evidence of Barrett esophagus, grade C or D esophagitis, or documented history of bleeding GI ulcers will identify patients for whom deprescribing is unlikely to be beneficial. Advice should be sought from gastroenterologists for these patients to assess ongoing risk factors.

Risk of GI ulceration and the need for gastroprotection with a PPI should be given careful consideration in patients receiving regular daily doses of nonsteroidal anti-inflammatory drugs (NSAIDs). Patients at high risk of GI ulceration include those with a history of a previous complicated ulcer or those with 3 or more risk factors (age older than 65 years; high-dose NSAID use; previous history of uncomplicated ulcer; concurrent use of acetylsalicylic acid [including low-dose acetylsalicylic acid], corticosteroids, or anticoagulants).[35,36] Patients at moderate risk of GI ulceration include those with 1 or 2 risk factors, while low-risk patients do not have any of these risk factors. Patients at moderate risk of GI ulceration taking chronic NSAIDs likely require a PPI or misoprostol, or can be treated with cyclooxygenase-2 inhibitors without a PPI. Patients at high risk should receive a cyclooxygenase-2 inhibitor plus a PPI or misoprostol.[35,36] Concomitant use of selective serotonin reuptake inhibitors and NSAIDs has also been associated with an elevated risk of upper GI bleeding.[37] Consideration could be given to using a PPI in such patients if both a selective serotonin reuptake inhibitor and NSAIDs are deemed necessary and the patient has other risk factors as described above.[37] For a more detailed overview of indications for gastroprotection, the reader is referred elsewhere.[35,36]

Once it is determined that a patient has been treated for a minimum of 4 weeks for GERD or mild to moderate (grade A or B) esophagitis and symptoms have resolved, deprescribing can be considered. Similarly, if a patient has completed treatment for known short-term indications like *Helicobacter pylori* eradication, intensive care unit stress ulcer prophylaxis, or uncomplicated peptic ulcer disease (without ongoing chronic NSAID use), the PPI should be deprescribed in accordance with practice guidelines for these indications.[10,38,39]

How should tapering be approached? Our systematic search did not identify trials that adequately addressed optimal tapering approaches to minimize symptom recurrence. There is very low-quality evidence that abrupt discontinuation (without tapering or using on-demand strategies) does increase symptom relapse. Therefore, it might be prudent to reduce the PPI to the lowest effective dose before discontinuation and to provide patients with a symptom management strategy that might include on-demand PPIs. Anecdotally, clinicians seem to prefer gradual dose reduction (eg, from twice daily to once daily, from high dose to low dose, from daily to every other day) and any of these approaches can be used, taking into consideration the patient's current medication supply, as well as the convenience of the approach.

Explaining the rationale for deprescribing PPIs, and the option of beginning with lowering the dose or using on-demand therapy, will facilitate patient and family acceptance.

What monitoring needs to be done and how often, and how should symptoms be managed? Follow-up times varied among trials of deprescribing.[40-50] Typically, patients attended follow-up appointments 4 and 12 weeks after deprescribing and again at 6 to 12 months. Patients also reported recurrence of symptoms by contacting their health care providers. Health care providers can consider following up with patients 4 weeks after deprescribing (or having patients contact them) to assess symptom control (heartburn, regurgitation, epigastric pain, dyspepsia, or pain on swallowing) and at 12 weeks after deprescribing to assess symptoms, frequency of on-demand use (if applicable), and the need for further investigation or a change back to continuous treatment.[40-50]

Differentiating "rebound hypersecretion" from symptoms of an underlying disorder such as GERD is challenging.[51] While studies of healthy volunteers taking PPIs have resulted in acid-related symptoms following deprescribing, the clinical significance remains unknown.[51-53] Regardless, we recommend monitoring for symptom recurrence and managing symptoms with on-demand PPIs, stepping down to H_2RA therapy (if appropriate, safe, and effective for the patient), other over-the-counter agents (eg, calcium carbonate), or nonpharmacologic approaches.

Some nonpharmacologic interventions have demonstrated reduction in symptoms, and these include weight loss, avoiding meals within 2 to 3 hours of bedtime, and raising the head of the bed.[54] Attention should also be paid to avoiding dietary triggers. In situations where symptoms continue to return despite use of on-demand or intermittent PPIs, the clinician should ensure testing for and treatment of *H pylori* has been completed.[55]

What other approaches help with PPI deprescribing? Inclusion of a pharmacist within the interdisciplinary team has been shown to reduce unnecessary PPI use and can facilitate patient education, dose changes, monitoring, and alerting the prescriber to ongoing symptoms.[56,57]

Clinical and stakeholder review

External clinical review of the guideline was conducted by a practising family physician and a pharmacist using

Box 5. Guideline endorsements

This evidence-based clinical practice guideline for deprescribing PPIs has been endorsed by the following groups:

- Canadian Association of Gastroenterology
- Canadian Nurses Association
- College of Family Physicians of Canada
- Canadian Pharmacists Association
- Canadian Society of Consultant Pharmacists
- Ontario Pharmacists Association
- RxFiles

PPI—proton pump inhibitor.

the AGREE II (Appraisal of Guidelines for Research and Evaluation) Global Rating Scale tool.[58] Relevant stakeholder organizations (ie, gastroenterology, family practice, pharmacy, and nurse practitioner) were invited to similarly review and endorse the guidelines (**Box 5**). Modifications were made to the original guideline draft to address reviewer comments.

How this deprescribing guideline relates to other clinical practice guidelines for PPI

Current GERD and peptic ulcer disease guideline recommendations support a short duration of PPI use and suggest attempting to discontinue PPIs in most patients or maintaining therapy at the lowest effective dose.[8,33] There is no information in current guidelines that assists clinicians with deprescribing PPIs (ie, tapering, discontinuation, or use of intermittent, step-down, or on-demand strategies). While a limited number of protocols for deprescribing PPIs have been proposed, there are no comprehensive evidence-based guidelines available for deprescribing PPIs.[57,59] A PPI deprescribing guideline works in conjunction with current treatment guidelines because it offers clinicians recommendations and clinical considerations to help them deprescribe PPIs in patients after an appropriate treatment duration or if long-term therapy is being reevaluated.

Guidelines for recommended PPI treatment duration. Guidelines for management of GERD suggest short-term treatment (4 to 8 weeks) for most patients.[8,33] After 4 to 8 weeks, in patients without a compelling indication for maintenance therapy (such as erosive esophagitis or Barrett esophagus), PPI therapy should be reassessed.[8,33] Canadian GERD management guidelines recommend that in individuals who have responded well to long-term PPI therapy (and who do not have an indication for maintenance therapy), the medication can be discontinued to assess the need for ongoing therapy (rated as poor-quality evidence).[33] If maintenance therapy is required, the medication should be instituted at the lowest possible dose, which includes on-demand therapy (recommendation derived from multiple randomized controlled trials, rated as fair-quality evidence).[33] The American College of Gastroenterologists 2013 guideline recommends PPI therapy for 8 weeks initially (rated as a strong recommendation with a high level of evidence derived from meta-analyses and randomized controlled trials), after which time the PPI should be discontinued in most patients and the need for maintenance therapy should be assessed.[8] If long-term PPI maintenance therapy is required, the lowest effective dose should be used, which can include reducing medication to on-demand or intermittent PPI use (a conditional recommendation based on a low level of evidence).[8]

Peptic ulcer disease treatment guidelines recommend short-term PPI use in most patients (2 to 12 weeks), after which time PPI therapy should be discontinued unless maintenance therapy is clearly indicated (for example, in patients with daily NSAID use who have GI risk factors).[10,38,39,60] These recommendations are based on randomized controlled trial data and systematic reviews. The American College of Gastroenterologists 2012 guideline on management of bleeding ulcers recommends stopping antisecretory therapy after *H pylori* eradication unless patients require NSAIDs (rated as strong, supported by high-quality evidence).[60]

Gaps in knowledge

Proton pump inhibitors are used for a number of reasons; however, most deprescribing research has been done in relatively healthy patients (primarily adults and younger elderly patients) with mild or moderate GERD or esophagitis only. In conditions for which PPI treatment is usually of limited duration (eg, intensive care unit stress ulcer prophylaxis, peptic ulcer disease, *H pylori* treatment) or uncertain effectiveness (eg, cough), there were no trials that compared a deprescribing approach with continuous PPI use. In addition, the optimal approach to deprescribing PPIs has not been evaluated (eg, tapering before stopping). Direct comparison of different deprescribing approaches (to one another and to continuous PPI use, as well as various tapering approaches and stepping down to H_2RA therapy) would be helpful to determine if there is a best approach. Trials examining the outcomes of deprescribing for the frail elderly or those with other conditions (aside from GERD or esophagitis) would help clinicians weigh the harms and benefits of deprescribing in patients who might also be at higher risk of adverse effects of continued PPI treatment. Studies employed different definitions of symptom relapse and patient satisfaction; consistency would be helpful to improve the quality of the body of evidence and should include patients' perspectives in terms of what is meaningful to them. Attention to both the positive (such as resolution of side effects

caused by the PPI) and negative (such as recurrence of upper GI symptoms) patient-specific effects of PPI deprescribing, particularly over the longer term, would be helpful. Evaluating cost-effectiveness and long-term medical resource use is also important.

Next steps

The deprescribing team will provide routine guideline updates as new evidence emerges that might change the recommendations. Prospective evaluation of the effects of adoption of this and other deprescribing guidelines will be part of a research strategy in the future.

Conclusion

Overuse of medication is acknowledged to be a key contributor to polypharmacy, with attendant negative effects on health. Proton pump inhibitors are commonly indicated for short-term use, and the potential for harm is not insignificant. A systematic review identified that PPIs can be safely deprescribed in many patients taking them for the common indications of GERD and mild esophagitis. This evidence-based guideline is the first in a series of guidelines aimed at helping clinicians make decisions about when and how to safely stop medications. Implementation of such guidelines will encourage clinicians to carefully evaluate the ongoing use of medications and potentially reduce the negative effects of polypharmacy.

Dr Farrell is Assistant Professor in the Department of Family Medicine at the University of Ottawa in Ontario, Adjunct Assistant Professor in the School of Pharmacy at the University of Waterloo in Ontario, and Scientist at the Bruyère Research Institute at the University of Ottawa. **Dr Pottie** is Associate Professor in the Department of Family Medicine and the School of Epidemiology, Public Health and Preventive Medicine at the University of Ottawa and Scientist at the Bruyère Research Institute. **Mr Thompson** was a master's student in the School of Epidemiology, Public Health and Preventive Medicine at the University of Ottawa at the time of guideline development. **Ms Boghossian** was a resident in the Department of Pharmacy at the Ottawa Hospital at the time of guideline development. **Ms Pizzola** was a project coordinator with the Bruyère Research Institute during guideline development. **Ms Rashid** was a resident in the Department of Pharmacy at the Ottawa Hospital at the time of guideline development. **Dr Rojas-Fernandez** was Schlegel Research Chair in Geriatric Pharmacotherapy at the Schlegel-UW Research Institute on Ageing and the School of Pharmacy at the University of Waterloo at the time of guideline development. **Ms Walsh** is a pharmacist with the Toronto Central Community Care Access Centre in Ontario. **Dr Welch** is Director of the Methods Centre at the Bruyère Research Institute and Assistant Professor in the School of Epidemiology, Public Health and Preventive Medicine at the University of Ottawa. **Dr Moayyedi** is Director of the Division of Gastroenterology at McMaster University in Hamilton, Ont.

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Contributors

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Competing interests

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Correspondence

Dr Barbara Farrell; e-mail **bfarrell@bruyere.org**

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