Gastroenterology 2022;■:1–9

CLINICAL PRACTICE UPDATE

AGA Clinical Practice Update on De-Prescribing of Proton Pump Inhibitors: Expert Review

Laura E. Targownik,[1] Deborah A. Fisher,[2] and Sameer D. Saini[3,4]

[1]Division of Gastroenterology and Hepatology, Department of Medicine, Mount Sinai Hospital, Temerty Faculty of Medicine at the University of Toronto, Toronto, Ontario, Canada; [2]Division of Gastroenterology, Department of Medicine, Duke University, Durham, North Carolina; [3]Veterans Affairs Center for Clinical Management Research, Ann Arbor, Michigan; and [4]Department of Internal Medicine and Institute for Healthcare Policy and Innovation, University of Michigan, Ann Arbor, Michigan

DESCRIPTION: Proton pump inhibitors (PPIs) are among the most commonly used medications in the world. Developed for the treatment and prevention of acid-mediated upper gastrointestinal conditions, these agents are being used increasingly for indications where their benefits are less certain. PPI overprescription imposes an economic cost and contributes to polypharmacy. In addition, PPI use has been increasingly linked to a number of adverse events (PPI-associated adverse events [PAAEs]). Therefore, de-prescribing of PPIs is an important strategy to lower pill burden while reducing real costs and theoretical risks. The purpose of this clinical update was to provide Best Practice Advice (BPA) statements about how to approach PPI de-prescribing in ambulatory patients. **METHODS:** Our guiding principle was that, although PPIs are generally safe, patients should not use any medication when there is not a reasonable expectation of benefit based on scientific evidence or prior treatment response. Prescribers are responsible for determining whether PPI use is absolutely or conditionally indicated and, when uncertainty exists, to incorporate patient perspectives into PPI decision making. We collaboratively outlined a high-level "process map" of the conceptual approach to de-prescribing PPIs in a clinical setting. We identified the following 3 key domains that required BPA guidance: documentation of PPI indication; identifying suitable candidates for consideration of de-prescribing; and optimizing successful de-prescribing. Co-authors drafted 1 or more potential BPAs, supported by literature review, for each domain. All co-authors reviewed, edited, and selected or rejected draft BPAs for inclusion in the final list submitted to the American Gastroenterological Association Governing Board. Because this was not a systematic review, we did not carry out a formal rating of the quality of evidence or strength of the presented considerations.

BEST PRACTICE ADVICE STATEMENTS

BEST PRACTICE ADVICE 1: All patients taking a PPI should have a regular review of the ongoing indications for use and documentation of that indication. This review should be the responsibility of the patient's primary care provider. **BEST PRACTICE ADVICE 2:** All patients without a definitive indication for chronic PPI should be considered for trial of de-prescribing. **BEST PRACTICE ADVICE 3:** Most patients with an indication for chronic PPI use who take twice-daily dosing should be considered for step down to once-daily PPI. **BEST PRACTICE ADVICE 4:** Patients with complicated gastroesophageal reflux disease, such as those with a history of severe erosive esophagitis, esophageal ulcer, or peptic stricture, should generally not be considered for PPI discontinuation. **BEST PRACTICE ADVICE 5:** Patients with known Barrett's esophagus, eosinophilic esophagitis, or idiopathic pulmonary fibrosis should generally not be considered for a trial of de-prescribing. **BEST PRACTICE ADVICE 6:** PPI users should be assessed for upper gastrointestinal bleeding risk using an evidence-based strategy before de-prescribing. **BEST PRACTICE ADVICE 7:** Patients at high risk for upper gastrointestinal bleeding should not be considered for PPI de-prescribing. **BEST PRACTICE ADVICE 8:** Patients who discontinue long-term PPI therapy should be advised that they may develop transient upper gastrointestinal symptoms due to rebound acid hypersecretion. **BEST PRACTICE ADVICE 9:** When de-prescribing PPIs, either dose tapering or abrupt discontinuation can be considered. **BEST PRACTICE ADVICE 10:** The decision to discontinue PPIs should be based solely on the lack of an indication for PPI use, and not because of concern for PAAEs. The presence of a PAAE or a history of a PAAE in a current PPI user is not an independent indication for PPI withdrawal. Similarly, the presence of underlying risk factors for the development of an adverse event associated with PPI use should also not be an independent indication for PPI withdrawal.

Proton pump inhibitors (PPIs) are among the most commonly used medications in the United States, if not the world. Observational studies have demonstrated that PPI use has increased over time and that 7%–15% of patients use these medications at any time, with the prevalence increasing to 40% for patients 70 years or older.[1–4] Approximately one-quarter of all patients who receive a PPI will continue to use them for at least 1 year.[5] Although PPIs are the treatment of choice for the management of acid-mediated upper gastrointestinal (GI) conditions, such as erosive esophagitis and peptic ulcer disease,[6–9] these agents are being used increasingly for less clear indications and for indeterminate durations. In a large observational study examining ambulatory visits of PPI users, nearly two-thirds had no clear indication for PPI use.[10] In this context, multiple national gastroenterology organizations have called for

Abbreviations used in this paper: **BPA, Best Practice Advice; GERD, gastroesophageal reflux disease; GI, gastrointestinal; PAAE, proton pump inhibitor–associated adverse event; PCP, primary care provider; PPI, proton pump inhibitor; RAHS, rebound acid hypersecretion; RCT, randomized controlled trial.**

0016-5085/$36.00
https://doi.org/10.1053/j.gastro.2021.12.247

limiting PPI use.[11–13] In addition, PPIs have been available over-the-counter in the United States since 2003; therefore, physicians may not be involved in a patient's decision to initiate therapy.[14]

As PPI use has become more common, the emerging literature has identified several adverse effects potentially linked to these drugs,[15,16] from chronic kidney disease to fracture to dementia and, most recently, COVID-19.[17–21] All studies to date reporting these specific associations have been observational and therefore cannot establish causality.[22] In contrast, randomized controlled trials (RCTs) comparing PPIs with placebo have not shown a higher rate of any adverse event among PPI users.[23] Nonetheless, this body of literature has raised concerns among prescribers and patients about the long-term safety of PPIs. This concern may promote inappropriate discontinuation of PPIs when a strong indication for use exists.[24] In this context, we developed a set of Best Practice Advice (BPA) statements about how to approach PPI de-prescribing—"the clinically supervised process of stopping or reducing the dose of medications when they cause harm or no longer provide benefit"—in ambulatory patients.[25]

Best Practice Advice 1: All patients taking a PPI should have a regular review of the ongoing indications for use and documentation of that indication. This review should be the responsibility of the patient's primary care provider (PCP).

To determine whether a PPI's potential benefits outweigh the potential harms, it is essential to know why the PPI was prescribed and the indications for continuing use. Without an ongoing indication or evidence of benefit for the prescribing indication, the PPI can only incur harm. These harms include pill burden, medication-related costs, and potential adverse effects related to long-term use. Therefore, clinicians should clearly document an acceptable indication for the drug and that the indication is ongoing. In the absence of an appropriate ongoing indication, the medication should be considered for de-prescribing.

Currently, most PPIs are prescribed by PCPs.[26] Although gastroenterologists may be consulted, they do not generally provide long-term follow-up for patients using PPIs for common indications (eg, uncomplicated gastroesophageal reflux disease [GERD] and dyspepsia). PCPs are also likely the first physician point of contact for patients using over-the-counter PPIs. Therefore, we suggest that the PCP should be primarily responsible for reviewing the presence of ongoing indications for PPI use, and identifying candidates for de-prescribing. When a gastroenterologist is involved in the patient's care, we encourage documentation, as applicable, of indications for prolonged PPI use and clinical end points that signify PPI discontinuation. In health care settings with the infrastructure to review medication use, misuse, or overuse more broadly, a pharmacist- or nurse-specialist–centered multidisciplinary approach may facilitate systematic identification of inappropriate PPI use and de-prescribing.[27]

Best Practice Advice 2: All patients without a definitive indication for chronic PPI should be considered for trial of de-prescribing.

Definite and conditional indications for long-term and short-term PPI use are shown in Table 1. Multiple studies have found that patients often take PPIs in the absence of a continuing indication.[28–31] The vast majority of trials demonstrating efficacy have tested durations of 4–12 weeks,[32] or no more than 6–12 months for maintenance therapy.[33] Chronic PPI use may be unintended. For example, a PPI initiated in the hospital for an acute indication (eg, stress ulcer prophylaxis) may be continued at discharge without the review of indication and ongoing need suggested in BPA 1.[34] In addition, PPIs are frequently initiated without a definite indication, notably for empiric treatment of laryngopharyngeal symptoms of cough, throat clearing, globus, and voice hoarseness. Because an RCT has definitively demonstrated that PPIs have no benefit in the empiric management of these symptoms,[35] these patients should be considered for de-prescribing.

Best Practice Advice 3: Most patients with an indication for chronic PPI use who take twice-daily dosing should be considered for step down to once-daily PPI.

Double-dose PPIs (standard dose twice daily or a double-strength dose once daily) have not been studied in any RCT and are not US Food and Drug Administration–approved. Nonetheless, up to 15% of PPI users are on a higher-than-standard dose.[36] Higher-dose PPIs increase the costs of care and have been more strongly associated with certain complications, including community-acquired pneumonia, hip fracture, and *Clostridium difficile* infection; although there is no direct evidence of a causal relationship between PPI use and these adverse events.[37–39] There is evidence to support the use of higher doses of oral PPIs over standard dosing in the acute setting to prevent rebleeding from peptic ulcer disease.[40] However, there is minimal evidence to support their use for the maintenance of healed esophagitis or prevention of complications of peptic ulcer disease.

High-dose PPIs are often recommended in patients with suspected laryngopharyngeal reflux or Barrett's esophagus.[41,42] No study of Barrett's esophagus specifically demonstrates that double-dose PPIs are superior to standard-dose PPIs to prevent extension or progression to dysplasia or cancer. In addition, PPIs at any dose are ineffective in managing laryngopharyngeal symptoms.[35] High-dose PPIs are indicated for Zollinger-Ellison syndrome, which is exceedingly rare (1/1,000,000).[43,44] Therefore, most high-dose PPI users should be considered for stepping down to standard dosing.

In a trial of 117 patients using higher-than-standard doses of PPIs for GERD, 80% successfully stepped down to standard doses of PPI without significant recurrence of symptoms or the need to again increase the PPI dose.[45] Therefore, PPI dose de-escalation for GERD can be effective for the majority of users. It is unknown whether this success rate for de-escalation can be duplicated across other indications.

Best Practice Advice 4: Patients with complicated GERD, such as those with a history of severe erosive esophagitis, esophageal ulcer, or peptic stricture, should generally not be considered for PPI discontinuation.

Most patients with GERD have nonerosive disease.[46] However, approximately 20% of patients with untreated

Table 1. Indications for Proton Pump Inhibitor Use

Indications					
Definitely indicated for long-term use (>8 wk)	Conditionally indicated for long-term use	Not indicated for long-term use	Definitely indicated for acute/short-term use (≤8 wk)	Conditionally indicated for acute/short-term use	Not indicated for acute/short-term use
Barrett's esophagus Clinically significant (LA Classification grade C/D) erosive esophagitis Esophageal strictures from GERD (ie, peptic strictures) Zollinger-Ellison syndrome Eosinophilic esophagitis Gastroprotection in users of ASA/nonsteroidal anti-inflammatory drug at high risk for GI bleeding Prevention of progression of idiopathic pulmonary fibrosis	PPI-responsive endoscopy-negative reflux disease, with recurrence on PPI cessation PPI-responsive functional dyspepsia, with recurrence on PPI cessation PPI-responsive upper airway symptoms ascribed to laryngopharyngeal reflux, with recurrence on PPI cessation Refractory steatorrhea in chronic pancreatic insufficiency with enzyme replacement Secondary prevention of gastric and duodenal peptic ulcers with no concomitant antiplatelet drugs	Symptoms of nonerosive reflux disease with no sustained response to high-dose PPI therapy Functional dyspepsia with no sustained response to PPI therapy Steroid therapy in the absence of ASA/nonsteroidal anti-inflammatory drug therapy Prevention of recurrent upper GI bleeding from causes other than: Peptic ulcer disease, including gastric and duodenal erosions Erosive esophagitis	*Helicobacter pylori* eradication Stress ulcer prophylaxis for ICU patients with risk factors Uninvestigated GERD/dyspepsia Treatment of NSAID-related gastric and duodenal peptic ulcers	Initial or on-demand treatment of endoscopy-negative reflux disease Initial treatment of functional dyspepsia Uninvestigated dyspepsia Ulcer prevention after sclerotherapy or band ligation treatment of esophageal varices Prevention of rebleeding from Mallory-Weiss tears	Empiric treatment of laryngopharyngeal symptomatology Acute undifferentiated abdominal pain Acute nausea and vomiting not believed to be related to GERD/esophagitis Any isolated lower GI symptomatology

ASA, aspirin; ICU, intensive care unit; LA, Los Angeles.

GERD have erosive esophagitis.[47] Erosive esophagitis can lead to GERD-related complications, such as GI bleeding or stricture formation. PPIs have been shown to be effective in healing erosive esophagitis and in preventing the development and recurrence of complications of GERD in long-term users.[48] A history of erosive esophagitis is also more common among persons who are found to have Barrett's esophagus.[49] In addition, recurrence of esophagitis is common after withdrawal of treatment, particularly in those with more clinically significant disease (eg, symptomatic Los Angeles Classification grade C or D).[50]

Therefore, in patients with a known history of more severe erosive esophagitis (Los Angeles Classification grade C/D) or those with GERD-related complications, PPIs should generally not be considered for discontinuation unless the benefits and harms have been weighed and discussed with the patient. Because many patients with GERD are treated empirically, and even severe erosive esophagitis generally heals with PPI use without long-term sequelae, it may not be known whether a PPI user has had severe erosive esophagitis, or has a predisposition to developing more severe erosive esophagitis in the absence of ongoing PPI use. In these patients, de-prescribing can be considered, but PPI use should be quickly re-initiated in those who develop symptoms or signs suggestive of the emergence of complicated GERD, with consideration of upper endoscopy to confirm the presence of severe erosive esophagitis.

Best Practice Advice 5: Patients with known Barrett's esophagus, eosinophilic esophagitis, or idiopathic pulmonary fibrosis should generally not be considered for a trial of de-prescribing.

There are several conditions in which a trial of de-prescribing has the potential to cause greater harm than benefit and should therefore not be pursued. First, one key long-term complication of GERD is esophageal adenocarcinoma.[51] In patients with its known precursor lesion, Barrett's esophagus, there is evidence from both observational studies and RCTs that PPIs reduce the risk of esophageal adenocarcinoma.[52,53] Thus, patients with known Barrett's esophagus should not be considered for a trial of de-prescribing.

In patients with eosinophilic esophagitis, PPIs are often the first-line pharmacologic therapy.[54–56] With PPI therapy, clinical response and histologic remission have been observed in 61% and 51% of patients with symptomatic esophageal eosinophilia, respectively.[56] But not every patient with eosinophilic esophagitis requires a PPI, especially those who respond to other pharmacologic therapy (topical steroids) or to nonpharmacologic therapy.[57,58] However, de-prescribing the PPI in a patient who has previously responded may result in a high rate of symptomatic and histologic recurrence. The long-term consequences of untreated eosinophilic esophagitis are not well characterized, although some patients may develop fibrotic strictures, likely influenced by uncontrolled eosinophilic inflammation.[59]

In idiopathic pulmonary fibrosis, low-quality evidence suggests that PPIs reduce the likelihood of disease progression.[60–62] Until evidence comes to light that definitively demonstrates PPIs are ineffective in preventing idiopathic pulmonary fibrosis progression, we believe it is reasonable to not target these patients for PPI de-prescribing.

Best Practice Advice 6: PPI users should be assessed for upper GI bleeding risk using an evidence-based strategy before de-prescribing.

Best Practice Advice 7: Patients at high risk for upper GI bleeding should not be considered for PPI de-prescribing.

One of the key benefits of PPIs is that they markedly reduce the likelihood of upper GI bleeding.[63,64] Because risk factors for upper GI bleeding (such as concomitant over-the-counter aspirin use) are often "hidden," it is imperative that, before de-prescribing, patients be carefully assessed for such risk factors and overall upper GI bleeding risk to avoid adverse outcomes.[65–67]

The benefit of PPIs in ambulatory patients at elevated GI bleeding risk has been demonstrated in both RCTs and well-designed observational studies.[24,68–72] Despite these data, precisely which patients are at sufficiently increased risk for upper GI bleeding to warrant PPI co-therapy remains uncertain. Clearly, individuals with hypersecretory states, such as Zollinger-Ellison syndrome, should not be de-prescribed. But for others, multiple guidance statements offer varying recommendations, as shown in Table 2.[73–77]

Although these guidance statements differ, they generally indicate that patients are at high risk for upper GI bleeding if they have a history of upper GI bleeding, are taking multiple antithrombotics (including both anticoagulants and antiplatelets agents), or are taking aspirin or a nonsteroidal anti-inflammatory drug with an additional risk factor for upper GI bleeding (eg, older than 60 years, severe medical comorbidity, using second nonsteroidal anti-inflammatory drug or aspirin, taking an antithrombotic, or taking an oral corticosteroid). In such patients, the PPI should not be de-prescribed due to the sufficiently increased likelihood of future upper GI bleeding events.

Best Practice Advice 8: Patients who discontinue long-term PPI therapy should be advised that they may develop transient upper GI symptoms due to rebound acid hypersecretion.

Rebound acid hypersecretion (RAHS) is a physiologic phenomenon that can occur with discontinuation of prolonged PPI therapy.[80,81] PPIs inhibit gastric acid production, resulting in an increase in intragastric pH. At high pH levels, serum gastrin levels rise, as inhibition of gastric secretion normally only occurs in the presence of gastric acid.[82] Hypergastrinemia, in turn, promotes the proliferation of parietal cells and enterochromaffin-like cells; this, in turn, increases the capacity of the stomach to produce acid. As long as PPIs are continued, gastric acid secretion is held in check. However, once PPIs are discontinued, the acid-generating potential of the increased parietal cell mass is unleashed, potentially causing a profound decline in gastric acidity, which may promote the development of upper GI symptoms.[83–85] In a double-blinded RCT enrolling persons

Table 2. Examples of Guidance Recommendations for Proton Pump Inhibitor Gastroprotection

Group	Year	Clinical focus	Populations for whom PPI gastroprotection is recommended
ACG[75]	2009	NSAIDs	Patients using NSAIDs who are at moderate or high risk of upper GI bleeding (1 or more risk factors, including prior ulcer, older than 65 years, high-dose NSAID therapy, concurrent use of aspirin (including low-dose), corticosteroids, or anticoagulants).
ACP[77,78]	2010, updated in 2019	Prior upper GI bleeding	Patients with prior ulcer bleeding who require an NSAID (the NSAID should preferably be a COX-2 inhibitor).
ACCF/ACG/AHA[73]	2010	Antiplatelet therapy	Patients with a history of upper GI bleeding or with multiple risk factors for GI bleeding who require antiplatelet therapy. Risk factors include advanced age; concurrent use of anticoagulants, steroids, or NSAIDs, including aspirin; and *Helicobacter pylori* infection.
ESC/EACTS[74]	2017	Dual antiplatelet therapy	Patients using dual antiplatelet therapy.
ACCP[79]	2018	Atrial fibrillation	Patients using aspirin and an oral anticoagulant.
ACC[76]	2020	Antithrombotics	Patients on 2 or more antithrombotic agents.

ACC, American College of Cardiology; ACCF, American College of Cardiology Foundation; ACCP, American College of Chest Physicians; ACG, American College of Gastroenterology; ACP, American College of Physicians; AHA, American Heart Association; ESC, European Society of Cardiology; EACTS, European Association for Cardio-Thoracic Surgery.

without a history of upper GI symptoms, Reimer et al[84] demonstrated that PPI withdrawal after an 8-week course of PPI led to a higher incidence of upper GI symptoms compared with patients in whom PPI was continued. Although intragastric pH was not measured in this study, the findings are consistent with a role for RAHS in post-PPI withdrawal symptoms. The anticipated duration of RAHS after PPI withdrawal is not well characterized, although physiologic studies have suggested that enterochromaffin-like cells and parietal cell mass can still be present 8 weeks after PPI withdrawal, although they have usually regressed by 6 months after withdrawal.[80]

Inadomi et al[86] found that although approximately one-half of all patients with uncomplicated GERD who discontinued PPI were able to remain off PPIs 6 months later, three-quarters of those who successfully discontinued PPIs were using H2-receptor antagonists or over-the-counter antacids for symptom control. Therefore, we suggest that the use of as-needed H2-receptor antagonists and/or contact antacids for treatment of upper GI symptoms after PPI withdrawal would be reasonable. Similarly, using PPIs on demand in place of continuous PPIs provides effective symptom control, and could also be considered as a partial de-prescribing strategy.[87] A recent RCT also demonstrated that persons who do not have evidence of abnormal esophageal acid exposure (acid exposure time >4.0%) in the first 7 days after PPI withdrawal on ambulatory pH testing are much more likely to not require PPI re-initiation.[35] However, the feasibility of ambulatory pH testing before any attempt at discontinuation is unclear.

Therefore, patients who discontinue PPIs should be advised that they may experience upper GI symptoms at least in the short term, and that this does not necessarily mean they have to immediately return to using continuous PPIs. The use of on-demand PPIs, histamine type-2 receptor antagonists, or neutralizing antacids on an as-needed basis may be helpful for controlling symptoms in the short term without committing to continuous PPI therapy. Severe persistent symptoms lasting more than 2 months after PPI discontinuation may suggest the presence of a continuing indication for PPI therapy on a non–acid-mediated cause of symptoms.

Best Practice Advice 9: When de-prescribing PPIs, either dose tapering or abrupt discontinuation can be considered.

Because of concerns that symptoms occurring as a consequence of RAHS may be a barrier against successful discontinuation of PPI therapy, some have proposed using a tapering regimen in order to gradually decrease the profundity of acid inhibition, thus allowing for gradual regression of parietal cell hyperplasia while still affording some degree of control over acid secretion. There is 1 published trial that compared abrupt discontinuation of PPIs with a tapered dosing regimen over 3 weeks (PPI daily to PPI every other day for 3 weeks, then discontinuing), which showed no significant difference between the 2 study arms in the likelihood of remaining off PPIs and symptom free at 6 months (31% vs 22% for tapered vs abrupt discontinuation).[88] However, given that the regression of parietal and enterochromaffin-like cell hyperplasia may take 2–6 months to complete, it is possible that this tapering regimen was too rapid to be effective.

At this time, we suggest that tapering or abrupt discontinuation are reasonable; in either case, patients should be advised to be mindful of developing recurrent upper GI symptoms as a consequence of RAHS, and should try to manage with lower-potency options for symptom control.

Best Practice Advice 10: The decision to discontinue PPIs should be based solely on the lack of an indication for PPI use, and not because of concern for PPI-associated adverse events (PAAEs). The presence of a PAAE or a history of a PAAE in a current PPI user is not an independent indication for PPI withdrawal. Similarly, the presence of underlying risk factors for the development of an adverse event associated with PPI use should also not be an independent indication for PPI withdrawal.

Much of the increasing concern about PPI overuse and the need for de-prescribing has been driven by concern about PAAEs, including some associated with significant morbidity or mortality.[18,20,39,89–91] Much of the evidence linking PPI use to PAAEs has emerged from retrospective studies. However, these associations are not necessarily causal, and they can potentially be explained by residual confounding and other analytic biases.[22,92] Many of these associations between PPI use and PAAEs lack a plausible mechanism of action. Moreover, no RCT has yet demonstrated that PPI users have an increased incidence of any of the PAAEs.[23]

In spite of this, studies have shown that concern among patients about PPI-related complications is common, with nearly 40% having made an attempt at discontinuing PPIs, of whom 83% did so without being advised to by a physician.[93] Patients who reported "extreme concern" about PPI-related adverse effects were 20 times more likely to have tried to discontinue PPIs. More concerning, three-quarters of physicians reported that they have altered treatment plans because of concerns about PPIs, and approximately 80% state that they would discontinue PPIs after being presented with a clinical scenario of a patient at high risk of upper GI bleeding.[94] The discontinuation of PPIs in patients with definite indications on the basis of concern about the unproven risk may lead to both recurrent symptoms and serious complications in those with definite indications for PPI therapy. Therefore, physicians should not use concern about unproven complications of PPI use as a justification for PPI de-prescribing if there remain ongoing valid indications for PPI use.

Discussion

The decisions about PPI discontinuation are complex and nuanced, and consequences for inappropriate or poorly considered discontinuation can be significant. Conversely, the unchecked use of PPIs in situations when indications are absent or murky is a major contributor to health care costs, and even a small risk of medical harm is significant in the complete absence of benefit. We also recognize that PPI discontinuation requires a systematic approach, and that patients and their PCPs may not have the tools or resources to undertake this task in the face of competing medical concerns. We are hopeful that these BPA statements will be valuable to the clinician and patient in providing guidance for approach and decision making about this issue. We also encourage physicians to partner with pharmacists to implement these BPAs in their clinical settings.

References

1. Pottegard A, Broe A, Hallas J, et al. Use of proton-pump inhibitors among adults: a Danish nationwide drug utilization study. Therap Adv Gastroenterol 2016;9:671–678.
2. Daniels B, Pearson SA, Buckley NA, et al. Long-term use of proton-pump inhibitors: whole-of-population patterns in Australia 2013-2016. Therap Adv Gastroenterol 2020;13:1756284820913743.
3. Bustillos H, Leer K, Kitten A, et al. A cross-sectional study of national outpatient gastric acid suppressant prescribing in the United States between 2009 and 2015. PLoS One 2018;13:e0208461.
4. Lassalle M, Le Tri T, Bardou M, et al. Use of proton pump inhibitors in adults in France: a nationwide drug utilization study. Eur J Clin Pharmacol 2020;76:449–457.
5. Othman F, Card TR, Crooks CJ. Proton pump inhibitor prescribing patterns in the UK: a primary care database study. Pharmacoepidemiol Drug Saf 2016;25:1079–1087.
6. Chiba N, De Gara CJ, Wilkinson JM, et al. Speed of healing and symptom relief in grade II to IV gastroesophageal reflux disease: a meta-analysis. Gastroenterology 1997;112:1798–1810.
7. Yeomans ND, Tulassay Z, Juhasz L, et al. A comparison of omeprazole with ranitidine for ulcers associated with nonsteroidal antiinflammatory drugs. Acid Suppression Trial: Ranitidine versus Omeprazole for NSAID-associated Ulcer Treatment (ASTRONAUT) Study Group. N Engl J Med 1998;338:719–726.
8. Hawkey CJ, Karrasch JA, Szczepanski L, et al. Omeprazole compared with misoprostol for ulcers associated with nonsteroidal antiinflammatory drugs. Omeprazole versus Misoprostol for NSAID-induced Ulcer Management (OMNIUM) Study Group. N Engl J Med 1998;338:727–734.
9. Walan A, Bader JP, Classen M, et al. Effect of omeprazole and ranitidine on ulcer healing and relapse rates in patients with benign gastric ulcer. N Engl J Med 1989;320:69–75.
10. Rotman SR, Bishop TF. Proton pump inhibitor use in the U.S. ambulatory setting, 2002-2009. PLoS One 2013;8:e56060.
11. American Gastroenterological Association. Five things physicians and patients should question. Choosing Wisely. Released April 4, 2012. Available at:. https://www.choosingwisely.org/wp-content/uploads/2015/02/AGA-Choosing-Wisely-List.pdf. Accessed January 24, 2022.
12. American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc 2015;63:2227–2246.
13. Gastroenterology. Eleven things physicians and patients should question. Choosing Wisely Canada. Canadian Association of Gastroenterology, Canadian IBD Network for Research and Growth in Quality Improvement, Crohn's and Colitis Canada. Updated November 2021. Available at:. https://choosingwiselycanada.org/gastroenterology/. Accessed January 25, 2021.
14. Sheikh I, Waghray A, Waghray N, et al. Consumer use of over-the-counter proton pump inhibitors in patients with

gastroesophageal reflux disease. Am J Gastroenterol 2014;109:789–794.
15. Elias E, Targownik LE. The clinician's guide to proton pump inhibitor related adverse events. Drugs 2019; 79:715–731.
16. Vaezi MF, Yang YX, Howden CW. Complications of proton pump inhibitor therapy. Gastroenterology 2017; 153:35–48.
17. Targownik LE, Lix LM, Metge CJ, et al. Use of proton pump inhibitors and risk of osteoporosis-related fractures. CMAJ 2008;179:319–326.
18. Gomm W, von Holt K, Thome F, et al. Association of proton pump inhibitors with risk of dementia: a pharmacoepidemiological claims data analysis. JAMA Neurol 2016;73:410–416.
19. Xie Y, Bowe B, Li T, et al. Risk of death among users of proton pump inhibitors: a longitudinal observational cohort study of United States veterans. BMJ Open 2017; 7:e015735.
20. Klatte DCF, Gasparini A, Xu H, et al. Association between proton pump inhibitor use and risk of progression of chronic kidney disease. Gastroenterology 2017; 153:702–710.
21. Almario CV, Chey WD, Spiegel BMR. Increased risk of COVID-19 among users of proton pump inhibitors. Am J Gastroenterol 2020;115:1707–1715.
22. Ma C, Shaheen AA, Congly SE, et al. Interpreting reported risks associated with use of proton pump inhibitors: residual confounding in a 10-year analysis of national ambulatory data. Gastroenterology 2020; 158:780–782.e3.
23. Moayyedi P, Eikelboom JW, Bosch J, et al. Safety of proton pump inhibitors based on a large, multi-year, randomized trial of patients receiving rivaroxaban or aspirin. Gastroenterology 2019;157:682–691.e2.
24. Chan FK, Wong VW, Suen BY, et al. Combination of a cyclo-oxygenase-2 inhibitor and a proton-pump inhibitor for prevention of recurrent ulcer bleeding in patients at very high risk: a double-blind, randomised trial. Lancet 2007;369:1621–1626.
25. Linsky A, Gellad WF, Linder JA, et al. Advancing the science of deprescribing: a novel comprehensive conceptual framework. J Am Geriatr Soc 2019; 67:2018–2022.
26. Abrahami D, McDonald EG, Schnitzer M, et al. Trends in acid suppressant drug prescriptions in primary care in the UK: a population-based cross-sectional study. BMJ Open 2020;10:e041529.
27. Farrell B, Conklin J, Dolovich L, et al. Deprescribing guidelines: an international symposium on development, implementation, research and health professional education. Res Social Adm Pharm 2019;15:780–789.
28. Ladd AM, Panagopoulos G, Cohen J, et al. Potential costs of inappropriate use of proton pump inhibitors. Am J Med Sci 2014;347:446–451.
29. Heidelbaugh JJ, Kim AH, Chang R, et al. Overutilization of proton-pump inhibitors: what the clinician needs to know. Therap Adv Gastroenterol 2012;5:219–232.
30. Heidelbaugh JJ, Goldberg KL, Inadomi JM. Magnitude and economic effect of overuse of antisecretory therapy in the ambulatory care setting. Am J Manag Care 2010; 16:e228–e234.
31. Glew CM, Rentler RJ. Use of proton pump inhibitors and other acid suppressive medications in newly admitted nursing facility patients. J Am Med Dir Assoc 2007; 8:607–609.
32. 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; 5:CD002095.
33. Donnellan C, Sharma N, Preston C, et al. Medical treatments for the maintenance therapy of reflux oesophagitis and endoscopic negative reflux disease. Cochrane Database Syst Rev 2005;(2)CD003245.
34. Blackett JW, Faye AS, Phipps M, et al. Prevalence and risk factors for inappropriate continuation of proton pump inhibitors after discharge from the intensive care unit. Mayo Clin Proc 2021;96:2550–2560.
35. O'Hara J, Stocken DD, Watson GC, et al. Use of proton pump inhibitors to treat persistent throat symptoms: multicentre, double blind, randomised, placebo controlled trial. BMJ 2021;372:m4903.
36. Targownik LE, Metge C, Roos L, et al. The prevalence of and the clinical and demographic characteristics associated with high-intensity proton pump inhibitor use. Am J Gastroenterol 2007;102:942–950.
37. Dial S, Delaney JA, Barkun AN, et al. Use of gastric acid-suppressive agents and the risk of community-acquired Clostridium difficile-associated disease. JAMA 2005; 294:2989–2995.
38. Laheij RJ, Sturkenboom MC, Hassing RJ, et al. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. JAMA 2004;292. 1955–1560.
39. Yang YX, Lewis JD, Epstein S, et al. Long-term proton pump inhibitor therapy and risk of hip fracture. JAMA 2006;296:2947–2953.
40. Chen CC, Lee JY, Fang YJ, et al. Randomised clinical trial: high-dose vs. standard-dose proton pump inhibitors for the prevention of recurrent haemorrhage after combined endoscopic haemostasis of bleeding peptic ulcers. Aliment Pharmacol Ther 2012;35:894–903.
41. Shaheen NJ, Falk GW, Iyer PG, et al. ACG Clinical Guideline: diagnosis and management of Barrett's esophagus. Am J Gastroenterol 2016;111:30–50; quiz 51.
42. Kahrilas PJ, Shaheen NJ, Vaezi MF, et al. American Gastroenterological Association Medical Position Statement on the management of gastroesophageal reflux disease. Gastroenterology 2008;135:1383–1391; 1391.e1–e5.
43. Metz DC, Comer GM, Soffer E, et al. Three-year oral pantoprazole administration is effective for patients with Zollinger-Ellison syndrome and other hypersecretory conditions. Aliment Pharmacol Ther 2006;23:437–444.
44. Metz DC, Sostek MB, Ruszniewski P, et al. Effects of esomeprazole on acid output in patients with Zollinger-Ellison syndrome or idiopathic gastric acid hypersecretion. Am J Gastroenterol 2007;102:2648–2654.

45. Inadomi JM, McIntyre L, Bernard L, et al. Step-down from multiple- to single-dose proton pump inhibitors (PPIs): a prospective study of patients with heartburn or acid regurgitation completely relieved with PPIs. Am J Gastroenterol 2003;98:1940–1944.
46. El-Serag HB. Epidemiology of non-erosive reflux disease. Digestion 2008;78(Suppl 1):6–10.
47. Zagari RM, Fuccio L, Wallander MA, et al. Gastro-oesophageal reflux symptoms, oesophagitis and Barrett's oesophagus in the general population: the Loiano-Monghidoro study. Gut 2008;57:1354–1359.
48. Carlsson R, Galmiche J-P, Dent J, et al. Prognostic factors influencing relapse of oesophagitis during maintenance therapy with antisecretory drugs: a meta-analysis of long-term omeprazole trials. Aliment Pharmacol Ther 1997;11:473–482.
49. Hanna S, Rastogi A, Weston AP, et al. Detection of Barrett's esophagus after endoscopic healing of erosive esophagitis. Am J Gastroenterol 2006;101:1416–1420.
50. Vakil NB, Shaker R, Johnson DA, et al. The new proton pump inhibitor esomeprazole is effective as a maintenance therapy in GERD patients with healed erosive oesophagitis: a 6-month, randomized, double-blind, placebo-controlled study of efficacy and safety. Aliment Pharmacol Ther 2001;15:927–935.
51. Lagergren J, Bergström R, Lindgren A, et al. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med 1999;340:825–831.
52. Jankowski JAZ, de Caestecker J, Love SB, et al. Esomeprazole and aspirin in Barrett's oesophagus (AspECT): a randomised factorial trial. Lancet 2018;392:400–408.
53. Singh S, Garg SK, Singh PP, et al. Acid-suppressive medications and risk of oesophageal adenocarcinoma in patients with Barrett's oesophagus: a systematic review and meta-analysis. Gut 2014;63:1229–1237.
54. Hirano I, Chan ES, Rank MA, et al. AGA Institute and the Joint Task Force on Allergy-Immunology Practice Parameters Clinical Guidelines for the Management of Eosinophilic Esophagitis. Gastroenterology 2020; 158:1776–1786.
55. Molina-Infante J, Bredenoord AJ, Cheng E, et al. Proton pump inhibitor-responsive oesophageal eosinophilia: an entity challenging current diagnostic criteria for eosinophilic oesophagitis. Gut 2016;65:524–531.
56. Lucendo AJ, Arias Á, Molina-Infante J. Efficacy of proton pump inhibitor drugs for inducing clinical and histologic remission in patients with symptomatic esophageal eosinophilia: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2016;14:13–22.e1.
57. Kagalwalla AF, Sentongo TA, Ritz S, et al. Effect of six-food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis. Clin Gastroenterol Hepatol 2006;4:1097–1102.
58. Gonsalves N, Yang GY, Doerfler B, et al. Elimination diet effectively treats eosinophilic esophagitis in adults; food reintroduction identifies causative factors. Gastroenterology 2012;142:1451–1459.e1.
59. Dellon ES, Hirano I. Epidemiology and natural history of eosinophilic esophagitis. Gastroenterology 2018; 154:319–332.e3.
60. Dutta P, Funston W, Mossop H, et al. Randomised, double-blind, placebo-controlled pilot trial of omeprazole in idiopathic pulmonary fibrosis. Thorax 2019; 74:346–353.
61. Lee CM, Lee DH, Ahn BK, et al. Protective effect of proton pump inhibitor for survival in patients with gastroesophageal reflux disease and idiopathic pulmonary fibrosis. J Neurogastroenterol Motil 2016; 22:444–451.
62. Ghebre Y, Raghu G. Proton pump inhibitors in IPF: beyond mere suppression of gastric acidity. QJM 2016; 109:577–579.
63. Lanas A, Garcia-Rodriguez LA, Arroyo MT, et al. Effect of antisecretory drugs and nitrates on the risk of ulcer bleeding associated with nonsteroidal anti-inflammatory drugs, antiplatelet agents, and anticoagulants. Am J Gastroenterol 2007;102:507–515.
64. Lanas A, Garcia-Rodriguez LA, Arroyo MT, et al. Risk of upper gastrointestinal ulcer bleeding associated with selective cyclo-oxygenase-2 inhibitors, traditional non-aspirin non-steroidal anti-inflammatory drugs, aspirin and combinations. Gut 2006;55:1731–1738.
65. Adwani A, Bees N, Arnaout A, et al. Hemangioma of the breast: clinical, mammographic, and ultrasound features. Breast J 2006;12:271.
66. Hirschowitz BI, Lanas A. Intractable upper gastrointestinal ulceration due to aspirin in patients who have undergone surgery for peptic ulcer. Gastroenterology 1998; 114:883–892.
67. Lanas A, Serrano P, Bajador E, et al. Evidence of aspirin use in both upper and lower gastrointestinal perforation. Gastroenterology 1997;112:683–689.
68. Chan FK, Ching JY, Hung LC, et al. Clopidogrel versus aspirin and esomeprazole to prevent recurrent ulcer bleeding. N Engl J Med 2005;352:238–244.
69. Targownik LE, Al-Mamfud A. The prevalence of risk factors for gastrointestinal complications and use of gastroprotection among persons hospitalized for cardiovascular disease. Aliment Pharmacol Ther 2006; 23:743–749.
70. Targownik LE, Metge CJ, Leung S, et al. The relative efficacies of gastroprotective strategies in chronic users of nonsteroidal anti-inflammatory drugs. Gastroenterology 2008;134:937–944.
71. Bhatt DL, Cryer BL, Contant CF, et al. Clopidogrel with or without omeprazole in coronary artery disease. N Engl J Med 2010;363:1909–1917.
72. Ray WA, Chung CP, Murray KT, et al. Association of oral anticoagulants and proton pump inhibitor cotherapy with hospitalization for upper gastrointestinal tract bleeding. JAMA 2018;320:2221–2230.
73. Abraham NS, Hlatky MA, Antman EM, et al. ACCF/ACG/AHA 2010 Expert Consensus Document on the Concomitant Use of Proton Pump Inhibitors and Thienopyridines: A Focused Update of the ACCF/ACG/AHA 2008 Expert Consensus Document on Reducing the Gastrointestinal Risks of Antiplatelet Therapy and NSAID Use. Circulation 2010;122:2619–2633.
74. Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary

artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2017; 39:213–260.

75. Lanza FL, Chan FKL, Quigley EMM. Practice Parameters Committee of the American College of Gastroenterology. Guidelines for prevention of NSAID-related ulcer complications. Am J Gastroenterol 2009;104:728–738.
76. Kumbhani DJ, Cannon CP, Beavers CJ, et al. 2020 ACC Expert Consensus Decision Pathway for Anticoagulant and Antiplatelet Therapy in Patients With Atrial Fibrillation or Venous Thromboembolism Undergoing Percutaneous Coronary Intervention or With Atherosclerotic Cardiovascular Disease: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol 2021;77:629–658.
77. Barkun AN, Almadi M, Kuipers EJ, et al. Management of nonvariceal upper gastrointestinal bleeding: guideline recommendations from the International Consensus Group. Ann Intern Med 2019;171:805–822.
78. Barkun AN, Bardou M, Kuipers EJ, et al. International consensus recommendations on the management of patients with nonvariceal upper gastrointestinal bleeding. Ann Intern Med 2010;152:101–113.
79. Lip GYH, Banerjee A, Boriani G, et al. Antithrombotic therapy for atrial fibrillation: CHEST Guideline and Expert Panel Report. CHEST 2018;154:1121–1201.
80. Fossmark R, Johnsen G, Johanessen E, et al. Rebound acid hypersecretion after long-term inhibition of gastric acid secretion. Aliment Pharmacol Ther 2005;21:149–154.
81. Waldum HL, Arnestad JS, Brenna E, et al. Marked increase in gastric acid secretory capacity after omeprazole treatment. Gut 1996;39:649–653.
82. Sanduleanu S, Stridsberg M, Jonkers D, et al. Serum gastrin and chromogranin A during medium- and long-term acid suppressive therapy: a case-control study. Aliment Pharmacol Ther 1999;13:145–153.
83. Helgadóttir H, Lund SH, Gizurarson S, et al. Predictors of gastrin elevation following proton pump inhibitor therapy. J Clin Gastroenterol 2020;54:227–234.
84. Reimer C, Sondergaard B, Hilsted L, et al. Proton-pump inhibitor therapy induces acid-related symptoms in healthy volunteers after withdrawal of therapy. Gastroenterology 2009;137:80–87; 87.e1.
85. Niklasson A, Lindstrom L, Simren M, et al. Dyspeptic symptom development after discontinuation of a proton pump inhibitor: a double-blind placebo-controlled trial. Am J Gastroenterol 2010;105:1531–1537.
86. Inadomi JM, Jamal R, Murata GH, et al. Step-down management of gastroesophageal reflux disease. Gastroenterology 2001;121:1095–1100.
87. Pace F, Tonini M, Pallotta S, et al. Systematic review: maintenance treatment of gastro-oesophageal reflux disease with proton pump inhibitors taken 'on-demand. Aliment Pharmacol Ther 2007;26:195–204.
88. Björnsson E, Abrahamsson H, Simrén M, et al. Discontinuation of proton pump inhibitors in patients on long-term therapy: a double-blind, placebo-controlled trial. Aliment Pharmacol Ther 2006;24:945–954.
89. Freedberg DE, Kim LS, Yang YX. 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; 152:706–715.
90. Nochaiwong S, Ruengorn C, Awiphan R, et al. The association between proton pump inhibitor use and the risk of adverse kidney outcomes: a systematic review and meta-analysis. Nephrol Dial Transplant 2018; 33:331–342.
91. Freedberg DE, Salmasian H, Friedman C, et al. Proton pump inhibitors and risk for recurrent Clostridium difficile infection among inpatients. Am J Gastroenterol 2013; 108:1794–1801.
92. Targownik L. The importance of accounting for immortal time bias in pharmacoepidemiologic analyses. Am J Gastroenterol 2015;110:349.
93. Kurlander JE, Kennedy JK, Rubenstein JH, et al. Patients' perceptions of proton pump inhibitor risks and attempts at discontinuation: a national survey. Am J Gastroenterol 2019;114:244–249.
94. Kurlander JE, Rubenstein JH, Richardson CR, et al. Physicians' perceptions of proton pump inhibitor risks and recommendations to discontinue: a national survey. Am J Gastroenterol 2020;115:689–696.

Received June 19, 2021. Accepted December 10, 2021.

Correspondence
Address correspondence to: Laura Targownik, MD, MSHS, FRCPC, Mount Sinai Hospital, University of Toronto, 435-600 University Avenue, Toronto, Ontario, Canada M5G 1X5. e-mail: laura.targownik@sinaihealth.ca.

Acknowledgments
This expert review was commissioned and approved by the American Gastroenterological Association (AGA) Institute Clinical Practice Updates Committee and the AGA Governing Board to provide timely guidance on a topic of high clinical importance to the AGA membership, and underwent internal peer review by the Clinical Practice Updates Committee and external peer review through standard procedures of *Gastroenterology*.

Author contributions
All authors provided equal contribution to the writing of this manuscript.

Conflicts of interest
These authors disclose the following: Dr Fisher received funding from Exact Sciences for research, consulting, and Advisory Board participation; Guardant Health for Advisory Board participation; Freenome for research; and Takeda for research. Dr Fisher is currently employed by Eli Lilly and Company. None of these activities are related to proton pump inhibitors or medication de-prescribing. Dr Targownik has received investigator-initiated funding from Janssen Canada and served on advisory boards for AbbVie Canada, Takeda Canada, Merck Canada, Pfizer Canada, Janssen Canada, Roche Canada, and Sandoz Canada. She is the lead on an IBD Registry supported by AbbVie Canada, Takeda Canada, Merck Canada, Pfizer Canada, Amgen Canada, Roche Canada, and Sandoz Canada. The remaining author discloses no conflicts.

Funding
Dr Saini is funded by Veterans Affairs Health Services Research and Development to design and study the effects of programs to decrease inappropriate proton pump inhibitor use (SDR 18-151).