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The Use and Misuse of Proton Pump Inhibitors: An Opportunity for Deprescribing

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A B S T R A C T

Proton pump inhibitors (PPIs) are proven medications of choice for gastroesophageal reflux disease (GERD), acid-related disorders, erosive esophagitis, Barrett esophagus, prevention of gastrointestinal bleeding while on nonsteroidal anti-inflammatory drugs, eosinophilic esophagitis, peptic ulcer disease, stress ulcer prophylaxis in critically ill patients, and other indications. Best practice guidelines from several sources on the appropriate indications and duration of PPI therapy have been summarized for easy assimilation. Individualized decision with regard to PPI use is illustrated by case vignettes; best approaches are provided.

The significant increase in use of PPIs for ill-defined indications over the years, associated adverse outcomes with long-term use, and consequent increase in health care costs have drawn much attention. Adverse outcomes due to PPI therapy may be categorized as unrelated or related to gastric acid inhibition. Examples of outcomes unrelated to acid inhibition include allergic reactions, acute interstitial nephritis, chronic kidney disease, poor cardiovascular outcomes, dementia, and drug interactions; consequences of acid inhibition include gastrointestinal infections, pneumonia, nutrient deficiencies, fractures, spontaneous bacterial peritonitis, and small intestinal bacterial overgrowth.

Provider awareness regarding best practice guidelines on PPI use and imparting pertinent education to patients may be the rational approach to safe and effective PPI therapy. In individuals in whom the drug is not indicated, efforts at deprescribing the PPI may be attempted following discussion with the patient. Approaches include stopping the drug, reducing the dose or using "on-demand" therapy after completing the course of treatment for the specific indication. Barriers to successful deprescribing exist. Follow-up is recommended for recurrence of manifestations; in the event of recurrence, the PPI may need to be re-instituted.

PPIs are valuable, irreplaceable drugs in the prevention and treatment of certain disorders for specific durations of time. Evidence nevertheless suggests that excessive and inappropriately prolonged use of PPIs is associated with a broad range of adverse effects. Education of provider and patient, stewardship, and motivation are key to appropriate use of PPIs for the right indications. Key implications for practice are offered.

Proton pump inhibitors (PPIs) have been in use for more than 2 decades and are proven useful as medications of choice for gastroesophageal reflux disease (GERD), acid-related disorders, erosive disease, peptic strictures, Barrett esophagus, prevention of gastrointestinal bleeding while on nonsteroidal anti-inflammatory drugs (NSAIDs), eosinophilic esophagitis, and other indications.[1,2] The continuous increase in the use of PPIs in the past decade cannot be simply attributed to the substitution of histamine2 receptor antagonists (H_2RAs) by the more potent PPIs. Although PPIs are efficacious and appropriate for certain indications, there is little evidence to support their use for many other disorders; harms appear associated with long-term use, with a simultaneous increase in health care costs attributable to medication-related events, calling for interventions to improve prescribing practices.[3,4] Accordingly, there has been a

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significant growth in the literature pertinent to the use, efficacy, safety, and outcomes following PPI therapy.[4] Although the concerns regarding their use are growing, it is perhaps generally believed that PPIs are irreplaceable for the management of several disorders and the overall benefits with improvement in quality of life outweigh the potential harms from use.[5] Adhering to evidence-based guidelines may be the rational approach to safe and effective PPI therapy, although seldom accomplished in practice.[5]

Case Vignettes

The following case vignettes from practice involve decision making regarding PPI use.

Case 1, SH, 77-year-old woman, with history of polymyalgia rheumatica, hypertension, osteoporosis, B12 deficiency and type 2 diabetes (T2D); she was on omeprazole 40 mg daily for years for "gastroesophageal reflux disease" (GERD). Endoscopy recently confirmed gastritis and hiatal hernia. She is on risedronate, aspirin, and prednisone 5 mg daily, besides medications for hypertension and T2D. PPIs give her relief. What would be the approach to PPI use for her?

Case 2, EB, 75-year-old woman, with T2D, obesity, osteoarthritis, and hypertension, is on insulin, angiotensin-converting enzyme inhibitors, diuretics, antihypertensives, and analgesics, including periodic NSAIDs. She has an Hgb of 10 g/dL; ferritin and transferrin saturation are consistent with iron deficiency anemia. EB finally undergoes colonoscopy, which is negative; upper endoscopy confirms a gastric ulcer. She is in bereavement from loss of her husband from COVID-19 infection and has not returned to the gastroenterologist. What would be the role for PPIs in management?

Case 3, AA, an 85-year-old woman, has gait abnormalities due to cervical and lumbar stenosis; she has hypothyroidism, stage 3 chronic kidney disease (CKD) and a history of falls. AA uses cocktails of tramadol, ibuprofen, and lidocaine patch as needed and has been on omeprazole 40 daily for more than a year. Hgb is 10, with transferrin saturation of 20. At this age, she does not want an endoscopy. What would you tell her with regard to PPIs?

A guideline-based approach for the vignettes is offered in the section "implications for practice."

How Do PPIs Help?

Several drugs in the PPI class work similarly by inhibiting active parietal cell acid secretion. Stated simply, PPIs act by irreversible inhibition of H^+/K^+ ATPase, an enzyme (or proton pump) located in the gastric parietal cells that regulates acid production. PPIs inhibit acid secretion until replacement pumps are resynthesized; not all proton pumps are inhibited by a single dose, with some left uninhibited until further dosing. PPIs are administered typically one-half to 1 hour before breakfast for most efficient inhibition of proton pumps; it is in the fasting state that the H^+/K^+ ATPase is maximally present in parietal cells. PPIs differ in their pharmacokinetics, metabolism, and indications; the half-lives vary, some being short, leading to breakthrough manifestations at night, after dosing pre-breakfast in the morning.[2] In contrast to H_2RAs, PPIs have a better acid-suppressing capability; they maintain gastric acid pH >4 for 15 to 21 hours daily in contrast to about 8 hours from H_2RAs.[6] PPIs and H_2RAs are not prescribed concurrently to an individual.

The PPI Class of Drugs

PPIs are chemically benzimidazole derivatives. They are membrane permeable, acid-labile weak bases, available as tablets, capsules, or coated granules. Available PPIs include dexlansoprazole, esmoprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole. PPIs differ in their pharmacokinetics, metabolism, and indications; the half-lives vary, some being short, leading to breakthrough manifestations at night, after dosing pre-breakfast in the morning.[2] Although they have similarities, minor pharmacokinetic differences exist between them with respect to bioavailability, action, and exretion.[2] Following hepatic metabolism, the drugs are excreted through biliary and renal routes. The choice of a specific PPI has little clinical relevance in practice. Appropriate uses of PPIs based on indications and outcomes are the focus of this review.

All PPIs are approximately 95% to 97% protein bound and degraded by the P450 cytochrome system. Accordingly, they are subject to drug-drug interactions and differences in efficacy. Although overall effective, some individuals do not respond adequately or develop adverse events from a specific PPI. The variations in response among individuals is due to genotype variability of CYP2C19, the gene encoding the CYP450 isoenzyme responsible for PPI metabolism; the genetic variability is the rationale for individualizing PPI therapy.[7] Genotype-based dosing may help predict benefits and adverse outcomes for a given individual in future.[7]

Resident gut bacteria serve a purpose for the human host in promoting vital functions, such as defense against pathogens, energy production, immune regulation, and nutrient metabolism. Through mechanisms that may or may not relate to alterations in pH, PPIs have the potential to alter the normal bacterial milieu at the distal esophagus, stomach, small bowel, and colon; the consequences may be an alteration in risk for Barrett esophagus, changes in the upper gut bacteria, small intestinal bacterial overgrowth, and *Clostridium difficile* infection.[8] PPI-related microbiota alterations in each site of the gastrointestinal (GI) tract may also lead to increased susceptibility to or worsening of GI disorders.[9]

PPIs in Older Adults

With aging, pharmacokinetics and pharmacodynamics are altered in most individuals. In brief, although bioavailability is largely intact, there is a decline in hepatic and renal blood flow; phase I hepatic drug metabolism depends on blood flow and is more altered versus phase 2, affecting metabolism of phase 1 metabolized drugs. A decline in glomerular filtration rate and tubular secretion with age impairs renal-excreted drug removal. Decline in albumin levels (from disease rather than age) affects protein binding of drugs, raising free drug levels. These effects are further compounded by presence of multimorbidity, typical in the aged.[10,11] As a result, older adults are on multiple medications, some inappropriate in dosing and perhaps unnecessary. Polypharmacy, from a combination of prescribed and over-the-counter medications, is a forerunner of drug-drug, drug-nutrient, and drug-disease interactions with related adverse drug events.[10,11] PPI misuse may be one component of polypharmacy.

A study of 758 hospitalized patients, mean age 80.3 years, revealed that 232 patients were receiving PPIs; 195 (84%) were prescribed inappropriately. After reviewing the comorbidity and prescribed medications, the only independent predictor of inappropriate PPI use was the total number of received medications, calling for deprescription.[12] Among 69,352 older adults in a primary academic setting, 12.6% received PPIs; a review of PPI prescription was conducted in 399 patients for appropriateness consistent with guidelines, short or long term. Mean age of patients was 76.2 years, 63.9% women; 35.8% of prescriptions were potentially low value, some begun appropriately and then continued indefinitely. A fifth of physicians contributed to nearly three-fifths of low-value prescriptions.[13]

A review of 7 studies in hospitalized patients in the United States suggested similar, high rates of inappropriate use with low value, calling for educational programs to implement appropriate use.[14] Low-value prescriptions in this study referred to prescriptions that

Table 1
Best Practice Guidelines Regarding Use of PPIs[3–5,20]

Clinical Indication	Goals of Care and Duration of Use
GERD, acid-related: erosive esophagitis, peptic stricture[20]	• Short term for healing • Long term for symptom control
Uncomplicated GERD, for those who respond to short-term PPIs[20]	• Stop or reduce the PPI • If not possible, further evaluation before long-term therapy
Barrett esophagus and symptomatic GERD[20]	• Consider long-term PPI
Asymptomatic Barrett esophagus[20]	• Consider long-term PPI for symptom relief
High risk for ulcer bleeding while on NSAIDs[20]	• Use a PPI while the patient is on NSAIDs
Formulation of PPI[20]	• Do not choose a specific formulation based on potential risk
Patients on long-term PPIs[20]	• Need periodic reevaluation to determine lowest effective dose • Should not routinely use probiotics to prevent infection • Should not routinely increase calcium, vitamin B12, or magnesium intake above recommended dietary allowance • Do not routinely screen for bone density, serum creatinine, B12
Additional indications[3]	• Maintenance of healed EE • Nonerosive reflux disease (NERD) • Treatment of *Helicobacter pylori* infection in combination with antibiotics • Hypersecretory syndromes, including Zollinger Ellison syndrome • Critically ill patients on prolonged mechanical ventilation • Short term (with regular review) for functional dyspepsia
Gastroprotection[5]	• Steroid use not an indication, unless combined with NSAIDs
Refractory steatorrhea[5]	• PPIs may be added to pancreatic enzyme replacement
Appropriateness of PPI use and duration of therapy[4]	• Long-term use appropriate for Barrett esophagus, Zollinger Ellison syndrome PPI responsive eosinophilia, idiopathic peptic ulcer disease • Short-term therapy (4–12 weeks) for stress ulcer prophylaxis, *H. pylori* eradication, treatment of peptic ulcer disease, before endoscopy for acute upper GI bleeding, following endoscopy for upper GI bleeding
Inappropriate use of PPIs[4]	• Stress ulcer prophylaxis in non–critically ill patients • Corticosteroid use without concomitant NSAID use • Acute prophylaxis
Uncertain benefit[4]	• Nonresponsive GERD

lacked a guideline-based indication for short-term or long-term (>8 weeks) use; the usage was considered not significantly beneficial[14] and such prescriptions by primary care physicians appeared common in academic health systems.[14]

If providers of care prescribe inappropriately, what about the availability and risks of over-the-counter (OTC) PPIs for the short-term management of heartburn (2 weeks)? The trend of OTC use of PPIs appears to have increased markedly, in the absence of evidence-based recommendations. A panel of experts based on an evidence-based review and Delphi consensus determined that OTC use of PPIs is unlikely to mask the symptoms of esophageal or gastric cancer if used as directed, and that OTC PPIs are unlikely to affect micronutrient absorption, bone mineral density, or cause community-acquired pneumonia, *C. difficile* infection, or cardiovascular adverse events.[15]

A study of long-term PPI use in whole-of-population from Australia involved 4,388,586 persons on the medication; the highest use (prevalence of 33 − 43/100) was among those older than 65 years; median duration of therapy was 501 days, although several stepped down from higher to lower treatment strengths or intermittent therapy.[16] A review of 1.37 million prescriptions from Iceland over 13 years demonstrated an increase in overall outpatient use of PPIs; the prevalence increased with age, was more in women, and duration of use was higher with age, a third of users older than 80 years remaining on the medication after 1 year (compared with 13% of those 19 to 39 years); of note, the proportion of PPI users concurrently using NSAIDs decreased over the period.[17]

The excess inadvertent use of in-hospital initiated PPIs in low-risk patients outside critical care units is further associated with the continuation of PPIs in the outpatient setting following discharge, often in the absence of indications, increasing costs, with a potential for adverse outcomes.[18] The pattern continues in both community and long-term care sites. In a French study of 175 nursing homes, more than a third of residents were on PPIs; mean age was 86 years; of note, the vulnerable were more often on PPIs.[19] Peptic ulcer and NSAID use as indications accounted for a fraction of prescriptions, whereas most prescriptions were inappropriate in a setting of comorbidities and polypharmacy; the authors call for physician awareness about the health risks possibly induced by inappropriate PPI prescribing in nursing home residents.[19]

In summary, PPI overuse occurs in all settings; not uncommonly they are carried over from hospital to long-term or community care sites. Further, PPIs are used for guideline-based and ill-defined (off-label) reasons; the prescriptions initiated for acute or finite periods of time continue as chronic or long-term therapy, with potential for drug interactions and serious adverse outcomes.[11,18–20]

What Is Appropriate Use of PPIs?

Clinical Practice Guidelines (CPGs) on the appropriate use of PPIs and the duration of therapy when indicated have been outlined in several position papers.[3–5,20] The recommendations appear based on expert opinions and relevant published trials,[20] indications based on the Food and Drug Administration and National Institute for Clinical Excellence in the United Kingdom,[3] 3 Italian Scientific Societies,[5] and a review of appropriateness of PPI use based on 13 clinical scenarios.[4] The papers also considered adverse effects, nature of evidence, and risk estimates.[3–5,20] Table 1 incorporates best practice indications for PPI therapy from all 4 papers, providing the appropriate scenarios for PPI use, including the duration of therapy.

Although chronic PPI use appears associated with adverse outcomes, a reasonably optimal duration of therapy that is supposedly safe is not apparent for all indications. The conditions for which long-term therapy is supported include maintenance of symptom control in GERD, healing of erosive esophagitis, Barrett esophagus, NSAID or antiplatelet therapy with increased risk, and Zollinger Ellison syndrome.[3] Both NSAIDs and aspirin are often used chronically, and even if for relevant indications, adverse events such as ulcer or GI bleeding are a frequent occurrence, warranting prophylactic measures.

Although stress ulcer and GI bleeding prophylaxis with PPIs is resorted to in critically ill patients on ventilators, PPIs are not recommended in the non–intensive care unit settings for the same reason.[3] On the contrary, the reverse scenario also appears true. In a study of 181 hospitalized patients in France, 171 were older than 65 and 33% received PPI therapy, mostly already initiated in the outpatient setting; 21 of the 56 prescriptions (37.5%) were for an appropriate indication, confirming the high rate of inappropriate use.[21]

How adherent to practice guidelines are gastroenterologists and primary care providers? Gastroenterologists were more likely to adhere to best practices, although adherence was incomplete for both, with primary care physicians harboring more concerns regarding long-term PPI use and therapeutic decision making.[22]

As PPIs are also available OTC, their ease of access and use for short-term management of heartburn have increased, in spite of lack of evidence-based recommendations for benefits. A panel of experts reviewed the risks and benefits of OTC use of PPIs; their use appeared unlikely to mask the symptoms of esophageal or gastric cancer or adversely impact the natural history of precursor disorders, significantly impact nutrient status, cause pneumonia or *Clostridium difficile* infections, or cardiovascular events; however, they were more likely to cause infectious diarrhea, idiosyncratic reactions, and spontaneous bacterial peritonitis.[21]

Does PPI Use Influence Outcomes?

Numerous studies detail outcomes associated with PPI use. Several studies on outcomes are summarized in Table 2.[23–40] The prevalence and patterns of PPI use, and deprescribing efforts toward PPIs are presented in Table 3.[15,19,41–49]

Broadly, adverse outcomes associated with PPIs may be unrelated or related to gastric acid inhibition. Adverse effects unrelated to acid inhibition include allergic reactions, acute interstitial nephritis, CKD, cardiovascular outcomes, dementia, and drug interactions, whereas consequences of acid inhibition include gastrointestinal infections, pneumonia, nutrient deficiency (iron, calcium, magnesium, B12), fractures, spontaneous bacterial peritonitis, and small intestinal bacterial overgrowth.[23,25,26,28–31,35,36,50]

Musculoskeletal consequences have been associated with PPIs. A potential fracture risk has been suggested, although inconsistent; mechanisms involve increased hypochlorhydria and impaired mineral absorption.[32,38,39] Functional decline post hospital discharge has been attributed to PPIs.[24]

Although data outline the adverse or unwanted consequences, several contradictory reports mention the lack of harm.[25,27] A Canadian 3 × 2 randomized double-blind trial of 17,598 patients with stable cardiovascular and peripheral artery disease on rivaroxaban, aspirin, or the combination, placed on pantoprazole or placebo, were followed for a median 3 years; PPI use was not associated with any adverse event barring an increased risk of enteric infections.[27] Whether 3 years of follow-up is adequate to determine outcomes is questionable, with more than 5 years suggested as a better measure.[51] Reports on dementia or mild cognitive impairment from PPIs have not been substantiated by several studies,[28–30] although PPIs appeared to increase risk of pneumonia in patients with dementia.[31]

PPI usage and cardiovascular outcomes have drawn attention. PPIs may adversely affect vascular function; patients with GERD on PPIs have a 1.16-fold increased association with myocardial infarction and a twofold increase in cardiovascular mortality.[52] A large veterans longitudinal study observed that PPIs are associated with an excess mortality from cardiovascular disease (CVD) and CKD; further, in those without a documented indication for PPIs, there was excess mortality from CVD, CKD, and upper GI cancer.[37] Even after eradication of *Helicobacter pylori*, long-term PPI use may still be associated with an increased risk of gastric cancer.[53]

Certain infections, such as *Clostridium difficile* infections, small intestinal bacterial overgrowth, and community-acquired pneumonia, appear more common in long-term PPI users.[27,31] Of note, current PPI usage, short-term (<1 month) has been associated with worse outcomes of COVID-19 but did not increase susceptibility to the infection.[40]

It may be a perception in practice that intravenous formulation of a PPI is more efficacious than the oral form; a study of intravenous PPI versus oral PPIs for bleeding peptic ulcers following endoscopy demonstrated no differences with regard to rebleeding rates, need for surgery or transfusions, hospital length of stay, and mortality.[45]

Drug interactions between PPIs and vitamin K antagonists, antiplatelet agents, serotonin reuptake inhibitors, digoxin, medications for HIV disease, and immune-suppressants may result in increased or decreased efficacy of the medications.[54]

Minimize Misuse: An Opportunity for Deprescribing

Polypharmacy is common in older people; and PPIs are among the common misused medications. As an answer to polypharmacy, the concept of deprescribing medications, or deprescription, has gained acceptance in practice in recent years. “Deprescribing” is a programmed reduction in the drug number or dosage of inappropriate medications supervised by a health care professional, with a goal to reducing adverse outcomes.[48,55] The Choosing Wisely Canada recommendation on PPI therapy, updated in 2019, states: “Don’t maintain long-term PPI therapy for GI symptoms without an attempt to stop/reduce the PPI at least once per year in most patients”; those with Barrett esophagitis and gastrointestinal bleeding would be exempt.[55] A review by nurse practitioners states that guidelines are not always clear, although adherence is emphasized; education of both patient and practitioner is hence paramount.[56] Stewardship is helpful and recommended.[57]

To develop an evidence-based guideline, a group of 5 health care professionals (including family physician, gastroenterologist, and pharmacists) developed an algorithm plus guideline for deprescribing PPIs; options included reducing the dose, stopping the drug, or using “on-demand” therapy.[58] The recommendations were meant to assist and not dictate decision making for patients. The guideline recommends deprescribing PPIs in those who have completed a minimum 4-week course of treatment with resolution of upper GI symptoms, assuming there was no indication for long-term therapy. Stopping the PPI could be done abruptly or as a drug taper; intermittent PPI use was defined as daily intake for a predetermined finite period (of 2 to 8 weeks) until resolution of symptoms; on-demand use refers to discontinuing the drug until symptoms recur, at which time the drug is taken until symptoms resolve; or a lower dose, meaning a reduction from a standard maintenance dose.[58] An H_2RA may be offered as an alternative to PPI, although a weak recommendation.[58] The guideline was endorsed by several Canadian associations (including gastroenterology, nursing, family physicians, and pharmacists).[58] Pharmacist interventions can significantly promote the rational use of PPIs, decrease inappropriate use, and help address costs, as successfully demonstrated over years, in a tertiary setting in China.[59]

In principle, the deprescribing process is not difficult; in practice, barriers may exist for successful implementation. A performance improvement project on deprescribing of medications for long-term care and community patients suggested that deprescribing of at least 1 medication was possible in 90.1% of 383 encounters; PPIs were among the most successfully deprescribed medications, possible in 26.2% of encounters.[48] Figure 1, the algorithm used in the study, is modified to address the deprescribing of PPIs. In a Veterans Affairs long-term care setting, PPIs were deprescribed mostly within the first 28 days of admission.[46] It is equally important to ensure that the result is sustained, as PPI usage is known to climb back to baseline in due course.[60] Although education is helpful, a national Australian study

Table 2
PPI Use and Outcomes[23–40]

Author	Country	Type and Aim of Study	Findings
Dharmarajan TS et al (2008)[23]	US	Cross-sectional study, community and long-term care, 6 years, effects of PPIs on B12 status	659 adults, 60–102 years 26% on PPIs, 28% on HR_2As B12 status declined with prolonged PPI use >3 years, but not with HR_2As
Corsonello A et al (2014)[24]	Italy	PPI use and functional decline in older adults discharged from acute care hospitals, prospective study	11 geriatric and internal medicine acute care wards; mean age 79.2 years; outcome was loss of at least one activity of daily living from discharge to follow-up for 12 months; PPI use was associated with functional decline during 12 months of discharge
Alshamsi F et al (2016)[25]	Canada	Meta-analysis, 19 trials, 2117 critically ill patients, PPIs vs. H_2RAs to prevent GI bleeding	PPIs more effective than H_2RAs in preventing GI bleeding; did not significantly affect risk of pneumonia, mortality or length of intensive care unit stay.
Trifan A et al (2017)[26]	Romania	Systematic review and meta-analysis, PPI use and *Clostridium difficile* (CDI) infection; 1990–2017	PPI use associated with an increased risk for CDI infection. Prospective studies needed.
Moayyedi P et al (2019)[27]	Multi-country	Multiyear randomized 3 x 2 trial; 17,598 patients with vascular disease on PPI or placebo	Randomly assigned rivaroxaban with aspirin or rivaroxaban or aspirin. PPI (pantoprazole) not associated with adverse events over 3 years with the possible exception of an increased risk of enteric infections.
Goldstein FC et al (2017)[28]	NIH, US	Alzheimer disease center, PPIs and risk of dementia, mild cognitive impairment	Volunteers, baseline normal cognition, >50 y, 884 on PPIs, 1925 intermittently, 7677 never. PPIs not associated with greater risk of dementia or Alzheimer disease.
Gray SL et al (2018)[29]	US	Population-based, 3484 persons >65 years, in Integrated Healthcare, PPI use and dementia risk	Patients without dementia at outset, screened every 2 y for a mean follow-up of 7.5 y. 827 (23.7%) developed dementia; PPI use was not associated with risk of dementia even with high cumulative exposure.
Min L et al (2019)[30]	China	Systematic review, meta-analysis; PPI use and risk of dementia	6 cohort studies among PPI users compared to non-PPI users; no statistical association between PPI use and increased risk of dementia or Alzheimer disease
Ho S et al (2017)[31]	Taiwan	Retrospective cohort study; PPIs and risk of pneumonia in dementia	786 dementia patients with new PPI usage vs 786 dementia patients not on PPIs. PPI usage in dementia associated with 89% increase risk of pneumonia. Cholinesterase inhibitors and H_2RAs decrease pneumonia risk.
Maes ML et al (2017)[32]	US	PubMed search, 1990–2016 for long-term adverse effects of PPIs	PPI usage associated with osteoporotic fractures, CDI, pneumonia, vitamin B12 deficiency, kidney disease and dementia.
Bundhun PK et al (2017)[33]	China	11 studies, 84,729 patients; concomitant use of clopidogrel and PPIs vs clopidogrel alone for cardiovascular outcomes	29,235 on PPIs; compared clopidogrel + PPIs vs. clopidogrel alone after coronary angioplasty. Combined clopidogrel + PPIs associated with significantly higher adverse CV events such as myocardial infarction and stent thrombosis.
Demcsak A et al (2018)[34]	Hungary	Systematic review and meta-analysis; PPIs and CV risk on clopidogrel	156,823 patients; risk of major adverse cardiovascular events higher in PPI plus clopidogrel group, but significance disappeared in randomized controlled trials, with no effect of combined use of PPIs and clopidogrel, warranting no restrictions
Zirk-Sadowski J et al (2018)[35]	UK	Longitudinal analysis, for risk of pneumonia with PPI use	75,000 persons, 60 y and older, age- and sex-matched controls, on PPIs for a year or more. PPI use associated with a greater risk of pneumonia in second year of use.
Rodriguez-Poncelas A et al (2018)[36]	Spain	Population-based cohort, duration and dosing of PPIs with incident CKD	PPI use associated with higher risk of incident CKD, eGFR <60 ml/mt. Association greater for high doses, apparent after 3 months exposure.
Xie Y et al (2019)[37]	US	Veterans Cohort study; a longitudinal study for all cause and cause specific mortality with PPIs	New users of PPIs (157,625) vs. H_2RAs (56842), deaths per 1000 on the drug. PPIs associated with excess mortality from CVD and CKD. In those without indication for PPIs, excess mortality from CVD, CKD and upper GI cancer.
Brozek W et al (2019)[38]	Austria	National observational cohort study; PPI use and subsequent hip fracture	31,668 patients, ≥50 years, with first hip fracture analyzed retrospectively; low-dose PPIs were not associated with subsequent hip fractures, especially in women; but PPI use associated with increased risk for subsequent fracture in men. Benefit for PPIs only short-term after hip fracture.
Thong BKS et al (2019)[39]	Malaysia	Longitudinal study 5 y, PPI use and fracture risk	PPI use associated with elevated fracture risks in 14 studies; 4 reported no significant relationship; suggests a potential relationship with fracture risk.

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Table 2 (*continued*)

Author	Country	Type and Aim of Study	Findings
Lee SW et al (2020)[40]	Korea	Nationwide cohort study, SARS-COVID-19 outcomes with PPI use	132,316 patients tested for COVID, SARS-COV-2 positivity (primary) and clinical outcomes of COVID 19 (secondary); 14163 current PPI users, 6242 past users; current PPI users at higher risk for severe clinical outcomes of COVID-19 but not susceptibility to SARS-COV-2 infection

suggested that imposing restrictions on subsidized use of PPIs is even more effective.[49]

One concern is the PPI-induced gastrin elevation secondary to hypoacidity and the subsequent hypergastrinemia-related rebound hyperacidity and dyspeptic symptoms following discontinuation of the PPI; the long-term gastrin elevation may have carcinogenic effects, raising concerns about consensus for deprescribing strategies.[61]

Barriers to Deprescribing PPIs

Although the physician and patient may agree with the plan to deprescribe the PPI, barriers nevertheless exist in practice. Patients may firmly believe that PPIs improve quality of life and values; such individuals may prefer intermittent or on-demand PPI therapy rather than stopping completely.[58] There is always fear of recurrence of symptoms. Providers may not be well-versed with best practice guidelines and adverse events following use, encountering difficulty in justifying their decision.[25] Further, there is scarcity of quality evidence regarding discontinuation approaches; anecdotally the dose reduction approach may be preferred by practitioners.[58] An unclear aspect is the frequency of follow-up after deprescribing PPIs; every 4 to 12 weeks initially and less often thereafter may be prudent to observe for recurrence of symptoms and "rebound hypersecretion." Surprisingly, 65.2% of community adults older than 65 years

Table 3
PPIs: Patterns of Use, Value from Use and Deprescribing[13,19,41–49]

Author	Country	Type and Aim of Study	Findings
Mafi JN et al (2019)[13]	US	Value of PPIs in 69, 352 adults >65 years, 63.9% females, academic health system	Low value, lack of guideline-based use in 35.8%. Although PPI initiated in 82% appropriately, drug was continued long term without indication. Among 169 primary care physicians, 18.9% provided 59.2% of the low-value prescriptions.
de Souto Barreto P et al (2013)[19]	France	Cross-sectional study in nursing homes, prevalence of PPI use	175 nursing homes, 6275 residents, mean age 86 years, 73.7% women. PPI use prevalence 37.8%, most prescriptions inappropriate, vulnerable people more often on PPIs.
Burdsall DP et al (2013)[41]	US	22 Midwestern US nursing facilities, PPI prescriptions	1381 admissions, 1100 patients (79.7%) on PPIs. No appropriate diagnosis in 718 (65.3%) cases, with discordance with International Classification of Diseases diagnostic codes. Cost of PPIs over 18 months was $348,414.
Marcum ZA et al (2014)[42]	US	Health, Aging and Body Composition Study: Gastroprotection underuse in high risk NSAID users	Daily users of an NSAID, 2002–03, vs 2006–07 to review underusers of PPIs if on nonselective NSAIDs and at risk for peptic ulcer, or on COX-2 selective NSAIDS and aspirin, not on PPIs. Daily NSAID use decreased from 17.6 to 11.3%; gastroprotective agent underuse decreased from 23.5% to 15.1% over time. Prescription insurance mattered for gastroprotection.
Glew CM et al (2007)[43]	US	PPI use in newly admitted nursing facility residents	61% of 98 patients were on a PPI based on transfer orders from hospital; only 30 patients had an appropriate diagnosis for PPIs in the medical record.
Metaxas ES et al (2015)[44]	US	MEDLINE and CINHAL data base, US Veterans, use of PPIs	30 articles, rate of overuse of PPI 33%–67%. Total costs >$200,000 for over-the-counter costs and >$1.5 million based on average wholesale cost. Several costs of pneumonia and *C. difficile* diarrhea.
Tringali A et al (2017)[45]	Italy	Meta-analysis: comparisons of intravenous vs oral PPIs for bleeding peptic ulcer	9 randomized controlled trials, 1036 patients, intravenous vs. oral PPIs. No differences in rebleeding rates, need for surgery, blood transfusions, duration of hospital stay or 30 day mortality.
Linsky A et al (2011)[46]	US	Veterans on PPIs at admission to VA long-term care facilities	More than a quarter of participants on a PPI at admission to long-term care have it discontinued within 180 days; of these 43% within 28 days.
Turner JP et al (2017)[47]	Canada	Cross-sectional population-based study, awareness of deprescribing	Community adults, 2665, mean age 74.9 years. 65.2% aware of medication-induced harm. Only 6.9% recognized the term "deprescribing."
Dharmarajan TS et al (2020)[48]	US	PI project, to deprescribe medications, in long-term and community adults	383 encounters, mean age 78.2 years. Deprescribing of any medication possible in 90.1% of encounters, PPIs in 26.2% encounters.
Bruno C et al (2020)[49]	Australia	Population-based National Education initiative over 1 y, to reduce PPI use over 6 y, Choosing Wisely guidelines	Observed 12,040,021 dispensings to 579,594 people. Sustained 1.7% decline in monthly dispensing of standard strength PPIs; along with education tighter restrictions on subsidized use more effective.

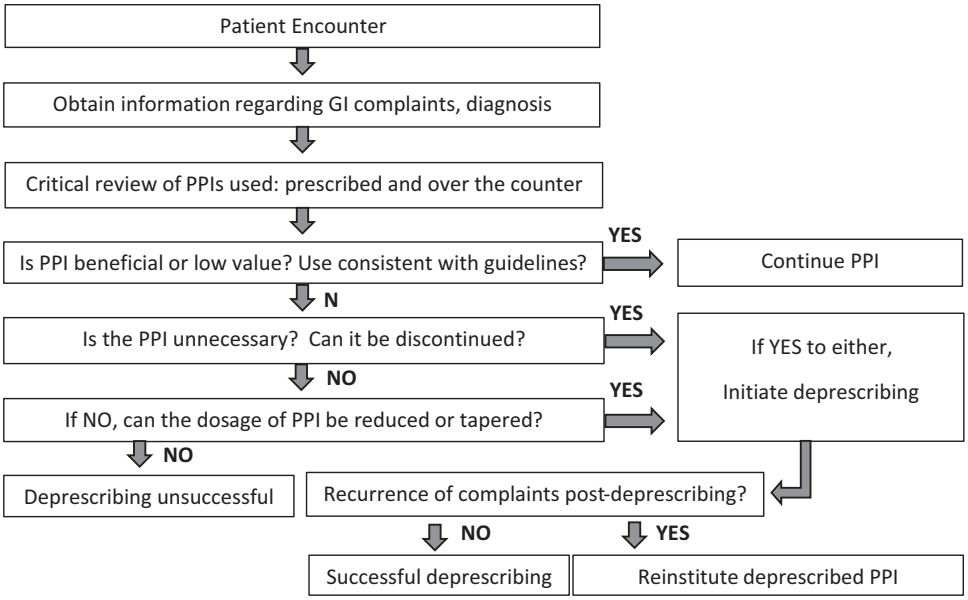

Fig. 1. Suggested deprescribing algorithm for PPIs[48] (modified from Dharmarajan et al.[48]).

were familiar with the concept of medication-induced harm, although not with the term deprescribing, indicating the need to initiate discussions using the language "medication harms" before drug taper.[47] Inadequate health care provider motivation, inertia, and a lack of time may be barriers, whereas favorable provider-patient relationship is a facilitator.[48]

Implications for Practice

Based on CPGs, the case vignettes illustrate the need for individualized PPI therapy. *Case 1 (SH)* has been on PPIs for too long for a diagnosis of hiatal hernia and gastritis and perhaps nonresponsive GERD; she has B12 deficiency and osteoporosis, both may relate to PPI use; low-dose steroids is not an indication for PPI therapy. Discussion must involve PPI taper over weeks or alternatively, intermittent use for finite periods of time.[4]

Case 2 (EB) is anemic; upper endoscopy confirmed a gastric ulcer; she has perhaps had mild upper GI blood loss. Ideally, she must avoid NSAIDs; if insistent on use, she is at high risk for bleeding and is a candidate for PPI prophylaxis as long as she is on NSAIDs.[20]

Case 3 (AA) has chronic painful lumbosacral disease and uses NSAIDs and other analgesics; she has CKD and iron deficiency anemia. She has refused endoscopy. Although omeprazole is acceptable for the short term, she must be deprescribed off NSAIDs in view of anemia and CKD, at which time she can also come off omeprazole.[20] She was open to discussions for surgery and physiotherapy as options.

The minority of studies suggesting the safety of long-term PPI use are overshadowed by the overwhelming evidence-based data implying numerous adverse events associated following use. Undoubtedly, PPIs have an important role in management, for prophylaxis and therapy. Acid suppression is clearly indicated for a certain duration of time for many disorders. Nevertheless, the use of acid blocking agents appears to be an answer to a panacea of GI complaints without evidence for benefit, although there is potential for harm. PPIs are often used far beyond the duration recommended for the indication, with potential for harm and economic implications, but there is little evidence regarding significant clinical harms from deprescribing PPIs.[58]

A recent editorial with regard to deprescribing PPIs, states we must overcome resistance (to deprescribing); that an attempt at deprescribing can be successful in any setting; any clinician with time, knowledge, and motivation can deprescribe PPIs, whether a cardiologist, hospitalist, family physician, or a nurse practitioner.[62] After abrupt PPI discontinuation, rebound hyperacidity may develop even after months; although there is no evidence, tapering over weeks mitigates this; and annual reassessment for ongoing requirements is reasonable.[62] Table 4 provides a summary of key points for prescribing and deprescribing PPIs.

Table 4
Key Points for Prescribing and Deprescribing PPIs In Practice

- Practicing physicians require to be educated on the current best practice guidelines regarding indications for PPI use and duration of therapy[3–5,20]
- Providers must become cognizant of the possible adverse outcomes following PPI therapy and the disorders that are not considered indications for use.
- Prescriptions for defined indications must be in the lowest dose for the shortest duration.
- Knowledge base regarding PPIs must be extended to patients on prolonged PPI therapy in a comprehensible manner.
- If use appears unjustified, a discussion between healthcare provider and patients must follow regarding consideration and steps for deprescribing.
- Options include discontinuing the drug, reducing dosage or "on-demand" therapy, factoring the indications and wishes of the individual.[58]
- The patient must be provided time to consider the options, must be assisted and not compelled. Deprescribing is seldom urgent in most instances.[48]
- Follow-up is important to determine the success or negative consequences following deprescribing.
- In future, genotype-guided dosing may offer safer approaches to prescribing.
- Motivation is a key factor for successful deprescribing.
- Any clinician with time, knowledge and motivation can deprescribe PPIs, whether a cardiologist, hospitalist, family physician or a nurse practitioner.[62]

"First do no harm; if a little is good, a lot is not necessarily better!"

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