Discontinuing Long-Term PPI Therapy: Why, With Whom, and How?

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Proton pump inhibitors (PPIs) are among the most widely used class of drugs prescribed over the long term in all of clinical medicine with 8–10% of ambulatory adults have been prescribed a PPI in the past 30 days. However, numerous studies have raised doubts about the long term safety of PPI use. The purpose of this review is threefold: (i) To provide an overview of the current evidence demonstrating associations between PPI use and adverse health outcomes and the likelihood of the associations being causal (Why?); (ii) To be able to identify long-term PPI users in whom the intensity of PPI therapy could be reduced or in whom PPIs could be eliminated outright (Who?); and (iii) To provide strategies on how to reduce or stop chronic PPI therapy while maintaining symptom control and reducing the risk for symptom or upper GI disease recurrence (How?).

INTRODUCTION

The introduction of proton pump inhibitors (PPIs) in the mid-1980s into the marketplace represented a major step forward in the management of acid-peptic-related disease. By irreversibly blocking the proton pump in the gastric oxyntic mucosa, PPIs irreversibly block active proton pumps in the gastric oxyntic mucosa, resulting in a profound reduction in basal and stimulated gastric acid output (1). As a result, the intragastric pH can be maintained at a sufficiently high level to allow for consistent healing and prevention of esophagitis and peptic ulcer disease, and more rapid control of associated symptoms (2,3). PPIs are also perceived to have a favorable side effect profile, and are often prescribed not only for established acid-related upper gastrointestinal (GI) disease but also empirically for nonspecific upper GI symptoms (4–6). As a result, PPIs have become among the most widely used class of drugs prescribed over the long term in all of clinical medicine. It is estimated that 8–10% of ambulatory adults have been prescribed a PPI in the past 30 days (7). PPI use is particularly prevalent in the elderly; people over the age of 60 years are 3.5 times more likely to be using PPIs than those under 60 years (8). In 2009, over US$7 billion was spent on PPI prescriptions in the United States, and over US$13 billion was spent worldwide (9) and this does not include money spent on over-the-counter PPIs (10).

However, numerous studies have raised doubts about the long-term safety of PPI use (11,12). As a result, many practitioners are looking for guidance of whether patients who have been using PPIs chronically should be curtailing their use. This decision is dependent of the indications for PPI use, and an assessment and balancing of the risks and benefits of reducing or eliminating PPI use in an individual patient. Also, if the decision is made to discontinue chronic PPI therapy, consideration needs to be given as how this process should be undertaken. The purpose of this review is threefold:

1. To provide an overview of the current evidence demonstrating associations between PPI use and adverse health outcomes and the likelihood of the associations being causal (Why?).
2. To be able to identify long-term PPI users in whom the intensity of PPI therapy could be reduced or outright eliminated (Who?).
3. To provide strategies on how to reduce or stop chronic PPI therapy while maintaining symptom control and reducing the risk for symptom or upper GI disease recurrence (How?).

WHY SHOULD WE BE CONCERNED ABOUT LONG-TERM PPI USE?

To date, published studies have reported association between the long-term use of PPIs and over two dozen unique complications (13–24) (Figure 1). The specific details regarding the studies reporting associations between PPI use and these conditions will not be described in detail in the article; the reader is directed to several excellent reviews of this topic ((25,26)).

However, one key commonality of these studies demonstrating PPI-associated adverse events is that they are nearly all observational studies, with the majority of the most cited and noteworthy studies having been performed by retrospectively analyzing large
health-care utilization data sets which had been collected primarily for administrative purposes. In an observational study, the exposure status (i.e., PPI user vs. PPI non-user) is not randomly assigned, and these non-random factors that lead to PPI use (or non-use) may individually impact on the probability of that person developing the outcome of concern. This issue of confound-
ing affects every observational trial, and it becomes impossible to
definitely prove whether the PPI caused the outcome, or whether
the factors that led to PPI use caused the outcome. While statisti-
cal tools such as multivariable regression and propensity weighting
can be used to mitigate against the effects of confounding, there
will invariably remain some degree of residual confounding due to
the presence of unmeasured differences in the exposed and non-
exposed groups. To unequivocally prove that PPIs are directly responsible for
any of the hypothesized complications, a randomized controlled
trial must be performed. However, it is exceedingly unlikely at this
time that a randomized controlled trial will be undertaken that is
sufficiently powered and of a sufficiently long duration to detect
a clinically and statistically significant increase in the incidence
of these complications between PPI users and non-users. How-
ever, a causal relationship can potentially be presumed if there are
other evidentiary pathways linking PPI use to a specific compli-
cation, as is the case how we are comfortable stating that there is
a causal association between cigarette smoking and lung cancer
even though there has never been a study where persons at risk
for lung cancer were randomized to cigarette use or matching pla-
cebos (27).

The Bradford Hill Criteria (Table 1) were conceived to provide
a framework for determining the likelihood of causality where an
association between an exposure and outcome is detected (28). While Hill originally proposed nine criteria for assessing the likeli-
hood of causality, the areas where there is universal agreement as
to their importance are those of strength of association, biologic
plausibility, consistency, and temporality

**Strength of association**
The greater the magnitude detected association between an expo-
sure and an outcome, the more likely that relationship is to be
causal and clinically relevant Strong associations that remain
between an exposure and outcome after adjusting for known con-
founders are less likely to due to the effect of residual unmeas-
ured confounders, and thus more likely to be real. Unmeasured
confounders are those factors that are associated with both PPI
use and the adverse event under study, but are either impossible
to assess or difficult to measure accurately. As an example, global
frailty increases the risk of hip fractures and is associated with
degenerative diseases and senescence; people who are frail are
also more likely to be prescribed PPIs (29,30). While as clinicians
we may subjectively recognize when a patient is frail, it is diffi-
cult to quantify precisely, and is therefore not generally reported in the
data sets in which these studies are performed.

This issue is distinct from that of statistical significance, which
can be attained for small magnitude effects if the sample size of
the population under study if sufficiently large. This is particularly
relevant given the epidemiologic studies reporting PPI-related
complications are performed on data sets containing information
on thousands if not millions of people, meaning that highly sta-

tistically significant results can be reported for very small asso-
ciations. Table 2 contains the reported effect sizes (odds ratios,
hazard, ratios, or risk ratios) of PPI exposure and the specific

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**Table 1. Bradford Hill Criteria**

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Strength of Association</th>
<th>Biologic Plausibility</th>
<th>Temporality</th>
<th>Consistency</th>
<th>Biologic Gradient</th>
<th>Coherence</th>
<th>Analogy</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strength of Association</td>
<td>Larger effect sizes are less likely to be due to chance or confounding</td>
<td>Evidence for a plausible physiologic mechanism should exist, or be thought possible</td>
<td>The exposure must occur prior to the event</td>
<td>Results across studies in similar populations should be similar</td>
<td>Strength of Association should correlate with exposure intensity</td>
<td>Presence of association does not directly contradict pre-existing evidence</td>
<td>Similar exposures have been shown to be cause similar disease processes</td>
<td>Other factors that would otherwise explain the association are not present</td>
</tr>
</tbody>
</table>

**Table 2. Most recent estimates of effect size for PPI-associated adverse events**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Effect size (95% CI)</th>
<th>Reference</th>
<th>Heterogeneity?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enteral infection</td>
<td>OR 2.55 (1.53–4.26)</td>
<td>Leonard et al. (23)</td>
<td>Yes</td>
</tr>
<tr>
<td>Community-acquired pneumonia</td>
<td>OR 1.49 (1.16–1.92)</td>
<td>Lambert et al. (36)</td>
<td>Yes</td>
</tr>
<tr>
<td>Clostridium difficile-associated diarrhea</td>
<td>OR 1.26 (1.12–1.29)</td>
<td>Cao et al. (107)</td>
<td>Yes</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>OR 1.26 (1.16–1.36)</td>
<td>Zhou et al. (37)</td>
<td>Yes</td>
</tr>
<tr>
<td>Dementia</td>
<td>HR 1.44 (1.36–1.52)</td>
<td>Gomm et al. (16)</td>
<td>N/A</td>
</tr>
<tr>
<td>Vitamin B12 deficiency</td>
<td>HR 1.83 (1.36–2.46)</td>
<td>Jung et al. (108)</td>
<td>Borderline</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>RR 1.36 (1.07–1.72)</td>
<td>Nochaivong et al. (109)</td>
<td>Yes</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>OR 1.16 (1.09–1.24)</td>
<td>Shah et al. (22)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

HR, hazard ratio; N/A, not applicable; OR, odds ratio; PPI, proton pump inhibitor; RR, relative risk.
adverse events in the most recently published meta-analysis as of September 2017, or of single studies where just one study has been published. For all adverse events, the pooled adjusted effect size is <2, and for many of the most frequently studied associations, the reported effect sizes are <1.5. This level of association, even if highly statistically significant, can be explained away by the effects of unmeasured confounding, and do not let strong support for causality. Conversely, clinicians should be cognizant that even small magnitude effects, if truly causal, can have enormous impacts of population health if the exposure is highly prevalent, and the outcome is morbid, and not rare. As an example, if 15% of the geriatric population are chronic PPI users, and PPI use was directly responsible for 25% increase in the risk of hip fracture among chronic users, then PPI use would lead to an additional 45,000 hip fractures per year among people over age 65 years in the United States (31) and would be responsible for 1,500 additional deaths each year (32).

**Temporality**

It is unimpeachably true that a patient must be exposed to a putative risk factor before the occurrence of an adverse event in order to be implicated in its cause. Essentially all studies that have studied PPI-related adverse events attempt to assess PPI exposure before the event of interest. However, the precise date that a diagnosis of a putative complication occurs may not necessarily be the same as what is recorded in the study database. This is particularly the case for diagnoses, which are progressive and degenerative like Alzheimer’s-type dementia or osteoporosis, or those with a long preclinical prodrome, which may have an onset months to years before being clinically recognized (33). In more acutely occurring complications, early symptoms may be misdiagnosed as similarly presenting conditions, as community-acquired pneumonia may be initially misdiagnosed as an upper respiratory infection, congestive heart failure, or, if chest pain is a predominant feature, gastroesophageal reflux disease (GERD) (34). If a PPI is dispensed during this prodromal period, it may generate as association between PPI use and this adverse outcome which appears to be temporal, but in fact violates this assumption. This phenomenon is commonly referred to as **protopathic bias**.

**Consistency**

In order for a result to be consistent, the results of the epidemiologic studies performed in different populations should fund associations between PPI use and adverse events of comparable magnitude. Studies of the most widely evaluated PPI-associated adverse conditions (fracture, *Clostridium difficile* infection, community acquired pneumonia) have demonstrated some degree of heterogeneity; and also have not shown a consistent dose response effect (35–37). In addition, as there is not currently a requirement for preregistration of epidemiologic studies, it is very likely that studies which do not demonstrate an association between PPI use and an adverse event are not completed or published. Commonly referred to as the “file-drawer effect ((38)),” this means that positive studies tend to be available for meta-analysis, and the non-published negative studies do not get included, biasing the findings in favor of there being an effect when none exists.

**Biologic plausibility**

If PPIs do indeed directly cause any of the adverse events for which PPI use is associated, then it must result from their physiologic effects in the person using them. The physiologic effects of PPIs can be characterized into three categories: (1) effects resulting from decreased gastric acid output due to the direct effect of inhibition of proton pump-mediated gastric acid secretion; (2) inhibition of proton pumps found in other organ systems; (3) effects due to alteration of drug metabolism, leading to changes in the concentration and activity of other drugs or metabolites that affect bone metabolism.

(1) **Effects resulting from reduction of gastric acid secretion:** Of these categories, the most well understood effect is that of PPIs on blocking gastric acid output. The presence of gastric acid is often considered to be a nuisance due to its role in the pathophysiology of GERD and peptic ulcer disease. Further, although gastric acid is needed to convert inactive pepsinogen into the gastric protease pepsin, ingested proteins will still be completely digested in the absence of pepsin and gastric acid by pancreatic proteases. Therefore, one might think that pharmacological inhibition of gastric acid secretion would have minimal negative consequence.

However, the fact that gastric acid production has been evolutionary retained across nearly all vertebrates suggests that the ability to generate gastric acid provides a survival advantage, at least until modern times (39). Most probably, the benefits of gastric acid pertain to its ability to stabilize the gut microbiota by preventing colonization with acid-sensitive organisms and pathogens; interestingly, carnivorous and scavenging animals, who have a higher risk of exposure to pathogens, tend to have higher levels of gastric acid production than do herbivores or grazers (40). In humans, multiple studies have demonstrated that conditions which lead to a reduction in gastric acid output (atrophic gastritis, surgical gastrectomy) increase the risk of enteric infections with acid-sensitive organisms such as *Salmonella* and *Campylobacter* (41).

PPI use has been strongly associated with an increased risk of infection with *C. difficile* (35,42–44). However, ingested *C. difficile* organisms are acid resistant, and therefore a reduction in gastric acid itself should not result directly in an increased likelihood of *C. difficile* infection (45). However, PPIs have also led to significant alterations of the gut microbiota (46), with decreases in general biodiversity, increase in Firmicute phyla organisms, and a decrease in Bacteroides. These changes may create an environment where *C. difficile* is more likely proliferate leading to symptomatic infection in people who are already colonized with *C. difficile* organisms (47).

In addition, gastric acid has a role in facilitating the absorption of iron, calcium, and vitamin B12. Of these, the effects of gastric acid inhibition on calcium absorption are likely the most clinically relevant (48–50), given the important role that calcium has...
in bone homeostasis and in maintaining bone strength (51). While calcium is more soluble in increasingly acidic solutions, the effects of PPI use on calcium absorption are negligible in most circumstances (49,52,53). In addition, the majority of studies evaluating the relationship between PPI use and bone mineral density have not shown any effect of PPI use on bone strength or on the prevalence of osteoporosis (54,55). Therefore, there is minimal biologic plausibility for PPIs to promote osteoporosis related fracture, at least as mediated by reduction in gastric acid secretion.

(2) Effects from blockage of non-GI proton pumps: While PPIs primarily inhibit the action of the proton pumps found in the gastric oxyntic mucosa, vacuolar proton pumps that can be blocked by PPIs are found elsewhere in the body, particularly in bone osteoclasts and the distal tubules of the nephron (56,57). While blockage of renal proton pumps in animal models may lead to decreased renal acid secretion and cause a mild metabolic acidosis, it does not have any effect on glomerular function (58). Therefore, it is unlikely that this mechanism is responsible for the association between PPIs and chronic renal insufficiency. In the case of osteoclast-based proton pumps, inhibition should decrease bone resorption, resulting in increased bone mineral density.

(3) Other proposed mechanisms: In the studies that have linked PPI use to Alzheimer’s disease, and chronic renal insufficiency (16,24), the investigators have suggested pathophysiologic pathways that are independent of their main pharmacologic action. As an example, the PPI lansoprazole has been shown to increase the synthesis of certain amyloid-β protein, which is also elaborated in persons with Alzheimer’s disease (59). However, the studies supporting this and other mechanisms have not been demonstrated in animal models or humans, and also have not be widely replicated. In these cases, the evidence for biologic plausibility is the most tenuous.

In addition, PPIs are metabolized in the liver by enzymes in the cytochrome P450 family; competitive inhibition of these cytochromes could interfere with the metabolism and/or clearance of other drugs. The proposed mechanism for the apparent association between myocardial infarction and PPIs among clopidogrel users was that PPIs would prevent cytochrome P450 metabolized conversion of the prodrug form of clopidogrel into the active drug (60). However, the clinical significance of this mechanism is doubtful (61), given that prospective trials demonstrated no difference in adverse cardiovascular event rates between PPI users and non-users among persons who were exposed to clopidogrel (62,63).

Overall, while correlations between chronic PPI use and a diverse range of acute and chronic complications have been consistently demonstrated, there is insufficient evidence supporting a causal role for PPIs in the etiology of any of these conditions. The supporting evidence for infectious complications, specifically enteric infections, is the most compelling, whereas the evidence for extragastrointestinal complications whose pathophysiology should not be influenced by reduced acid secretion is especially weak. At this point, guidelines that do not suggest chronic PPI users should be screened for any of the PPI-associated disease, and it is not recommended to discontinue PPIs in persons who are already afflicted with any of the PPI-associated adverse events, nor should long-term PPI users receive specific treatment in an attempt to prevent any of the complications (12,64). As an example, it is not recommended that PPI users undergo screening for osteoporosis or undergo a fracture risk assessment just because they are PPI users, and there is no contraindication against PPI use among people with established osteoporosis or a history of hip fracture. However, one cannot prove that PPIs are entirely safe, and the data sources that would be required to prove the safety of PPIs are lacking. Therefore, it remains important not to inappropriately use PPIs, and specifically, to limit their use to persons with conditions where the benefits of PPI are well defined.

WHO SHOULD REMAIN ON LONG-TERM PPI THERAPY

Definite indications for long-term PPI therapy

Treatment of erosive esophagitis and prevention of relapse: Among persons with erosive esophagitis that completely healed on PPI therapy, the risk of endoscopic relapse is 72% for persons who stop using PPIs compared to 13% for those who continue PPI therapy during this period (65). Furthermore, PPIs are more effective than histamine-2 receptor antagonists (H2RAs) in maintaining symptom-free remission among person with healed erosive esophagitis (91% PPI vs. 62% H2RA, P<0.001) (65). The risk of relapse with PPI discontinuation is particularly high among persons with more severe forms of esophagitis. PPI discontinuation could be considered among persons with milder forms of erosive esophagitis (LA Class A/B), or in those persons where a major factor that predisposed an individual to erosive esophagitis (such as heavy alcohol use) has been eliminated.

Treatment of PPI-responsive esophageal eosinophilia (REE): Approximately 50% of persons with apparent eosinophilic esophagitis will have a clinical and histologic response to PPI therapy (66). These patients are referred to as having PPI-REE, or PPI-REE. Persons with PPI-REE have a high rate of symptomatic and/or clinical relapse when effective therapy is discontinued. Although the natural history of PPI-REE is not well defined, there is evidence that untreated or undertreated eosinophilic esophagitis may eventually result in chronic stricture (67). In addition, the long term risks associated with PPI use are likely less clinically significant than those resulting from long-term corticosteroid use, the most commonly utilized medical therapy for EoE. Therefore, the long-term use of PPIs in persons with eosinophilic esophagitis would seem to be reasonable.

Prevention of peptic ulcer disease and its complications: PPIs are highly efficacious in preventing gastric and duodenal ulceration in chronic users of nonsteroidal anti-inflammatory drugs (68,69). In epidemiologic studies, persons who used PPIs concomitantly with nonsteroidal anti-inflammatory drug therapy reduce the odds of being hospitalized for complicated peptic ulcer disease by between 50% and 80% (70–72). PPI-based gastroprotection is recommended for all chronic aspirin and/or nonsteroidal anti-inflammatory drug users who have risk factors that increase the
risk of peptic ulcer disease-related complications; these risk factors include concomitant use of antiplatelet and/or anticoagulants, concomitant use of systemic corticosteroids, age over 70 years, prior history of peptic ulcer disease, and the presence of severe medical comorbidities (71,73,74).

Prevention of progression of Barrett’s esophagus: Acid-induced esophageal injury is a major etiologic factor in the development of intestinal metaplasia, and has been implicated in the progression to dysplasia and neoplasia (75). There are conflicting reports about the benefits of PPIs in the prevention of esophageal adenocarcinoma, although there is a trend towards their being protective (76–78). All major guidelines on the management of Barrett’s esophagus strongly recommend PPI therapy, even in the absence of symptoms, to prevent progression of Barrett’s esophagus to dysplasia and esophageal adenocarcinoma (79,80).

Zollinger–Ellison Syndrome: Hypersecretion of gastric acid due to the unregulated release of gastrin from a gastrinoma is the cardinal feature of Zollinger–Ellison Syndrome. PPIs are the most effective therapy for control of complications of gastric acid secretion (81–83) While removal of the gastrinomatous tissue may allow for discontinuation of PPIs, this is not possible for persons with metastatic disease, or those with underlying multiple endocrine neoplasia type 1 (84). In these patients, long-term continuation of PPIs is of unquestioned value.

Possible indications for long-term PPI therapy
There are a number of indications where though PPI use may be effective in the short term, the benefits of continuing therapy are not well described. In these scenarios, withdrawal of PPIs in would be unlikely to be result in significant adverse events. For patients with these indications, n=1 trials of substitution of PPIs with less potent anti-secretory therapies like H2RAs, pain modulating agents like tricyclic antidepressants or selective serotonin reuptake inhibitors, or outright discontinuation should be considered.

Functional dyspepsia: PPIs are frequently prescribed for patients with dyspepsia, even if no ulcer is present. The most recent meta-analysis of studies comparing PPIs with placebo for functional dyspepsia showed response rates of 34% for PPIs and 25% for placebo (risk ratio (RR) 0.88, 95% confidence interval (CI): 0.82–0.94) (85). However, the maximum duration of therapy evaluated is 8 weeks, and it is unclear whether this efficacy benefit is maintained over time. As functional dyspepsia is a chronic condition with recurrent symptoms, persons with functional dyspepsia likely will use PPIs for longer periods of time, despite there being no evidence of continued benefit over the longer term.

Endoscopy-negative reflux disease: Persons with reflux-like symptoms but with no endoscopic evidence of erosive esophagitis who are given PPIs have higher levels of symptom relief when compared to placebo (RR 0.69, 95% CI: 0.65–0.78); H2RAs (RR 0.78, 95% CI: 0.62–0.97) or prokinetics (RR 0.72, 95% CI: 0.56–0.92) (86). However, there is no evidence for the benefit of PPI therapy over the long-term among patients with endoscopy-negative reflux disease. Persons with endoscopy-negative reflux disease are a heterogeneous group, including those who have non-erosive reflux disease and those with functional heartburn, who manifest reflux symptoms consistent with reflux but do not have physiologic evidence of reflux of acidic gastric contents in to the esophagus. PPIs are likely effective in the long term for the former, but they are less likely to be efficacious in those whose symptoms are not due to esophageal acid exposure (87).

Symptoms presumed secondary to laryngopharyngeal reflux: Laryngopharyngeal reflux (LPR) is often implicated in the etiology of chronic symptoms of laryngopharyngeal irritation such as hoarse voice, sore throat, or globus sensation (88). Current ENT guidelines recommend PPI therapy for persons with laryngeal symptoms presumed secondary to LPR, often at high dose and for durations of at least 3–6 months (89). However, the diagnosis of LPR is generally based on the finding of irritation of the posterior larynx and arytenoid cartilage on visual inspection, which poorly differentiates between laryngitis and those due to other causes, such as post-nasal drip or environmental allergens and irritants (90). Further, more accurate evaluations for physiologic reflux, such as pH monitoring or multichannel impedance are rarely done (91). The evidence supporting PPIs for treatment of LPR is at best conflicted, with the most recently published meta-analyses demonstrating PPIs were no better than placebo in achieving symptom improvement (defined as a 50% reduction in laryngeal symptoms (PPIs 42% vs. placebo 39%, difference 4%, 95% CI: 6–14)), and also were no different than placebo in improving the signs of presumed LPR on laryngoscopic examination (92).

Inappropriate PPI use
Inappropriate PPI use can be defined as use which either occurs in the absence of a known indication, or for use for a nonabsolute indication where a trial of PPI cessation has not been considered or attempted (93). All current guidelines recommend limiting PPI use to specific indication, and to use the smallest dose for the shortest duration required to adequately control symptoms. Even in the absence of definitive evidence of medical harm associated with PPI use, the excess cost associated with unnecessary therapy should be enough reason to make attempts to curtail the inappropriate PPI use.

In 2010, Heidelbaugh et al. (94) assessed PPI use and their indications in 946 patients in ambulatory care clinic, and found that over one-third of PPI users did not have a documented indication for ongoing use, and 10% were using for extraesophageal indications. Furthermore, nearly one-half patients did not have any documentation of the response to therapy having been re-evaluated at any point following PPI initiation. Patients without appropriate indications who were using PPIs, without an indication, spent approximately US$1,500 per year on PPIs. Similarly, Ladd et al. (95) found that among 201 persons who were newly prescribed PPIs on a in-patient medical ward, three-quarters had either no documented indication or an inappropriate indication for PPI, of whom 40% continued PPI therapy following discharge.

The factors that are driving the inappropriate initiation and/or failure to address the need for ongoing PPI therapy have not been systematically evaluated, although a model characterizing patient...
PPI deprescribing refers to a patient or physician effort to either discontinue PPIs outright, decrease exposure to PPIs by stepping down to a lower dose or intermittent/on-demand treatment regimen, or substituting PPIs with a less costly and/or less potent form of gastric acid inhibition. An attempt at PPI deprescription should be considered for all PPI users who do not have definite indications for long-term therapy (severe erosive esophagitis, high risk for aspirin/nonsteroidal anti-inflammatory drug-related complications, and Barrett’s esophagus), with the goal of therapy being to use the lowest dose of PPI necessary to control acid-related symptoms and/or mucosa damage.

**Effectiveness of step-down regimens**

On-demand therapy, where a patient uses PPIs only when symptoms occur and taken until symptoms are adequately relieved, is significantly more effective than placebo in providing adequate symptom relief (51% vs. 14%, P<0.0001) (96). A meta-analysis that included randomized controlled trials comparing continuing PPI use to on-demand PPI use or in persons with mild treatment-responsive GERD symptoms found that persons assigned to on-demand therapy has a significant increase in the risk of loss of symptom control (16% vs. 10%, RR 1.71, 95% CI: 1.31–2.11), while decreasing weekly pill intake by nearly 3.8 PPI doses per week (97). In a primary care-based Norwegian study of 2156 patients who had PPI-responsive GERD, persons randomized to receive ongoing management with H2RAs had a significantly lower rate of symptom control than did those maintained on regular PPI therapy (32% vs. 72%, P<0.0001) (98). While these findings seem to favor continuing therapy as opposed to stepping down, the majority of persons who were decreased to on-demand therapy continued to report adequate symptom relief, as did a meaningfully large minority of those given H2RAs.

Inadomi et al. (99) prospectively demonstrated that 80% of persons with controlled symptoms of GERD on higher-than-standard doses of PPIs could be stepped down to standard dose PPIs without developing significant recurrent symptoms. Aside from the exceedingly rare Zollinger–Ellison syndrome, there are no clinical scenarios that absolutely necessitate the use of higher-than-standard doses of PPIs. Therefore, dose reduction strategies should be considered for all persons who are using PPIs chronically at high doses.

**Total discontinuation of PPIs**

In persons without a clear indication for PPI therapy, or in those persons who were treated empirically for upper GI symptoms, a trial of discontinuation can be attempted. Not surprisingly, persons with mild esophagitis who initially responded to PPI therapy who were given placebo had a relapse rate between 48 and 100% over the next 6 months, compared with 17–33% for those who continued on standard dose PPI (100).

For patients who are taking PPIs for unclear indications, or for symptoms where there is little evidence for PPI use, common sense would dictate that they should be discontinued without the expectation of adverse consequences. However, the sudden discontinuation of PPIs may cause a sudden and profound rise in gastric acid output, a phenomenon known as rebound gastric acid hypersecretion. The regular use of PPI raises intragastric pH; at high pH levels, the secretion of the trophic hormone gastrin is not negatively inhibited, predisposing to the development of hypergastrinemia that in turn stimulates oxyntic cell proliferation and an increased capacity to generate gastric acid (101). So long as the PPI is being taken, this increased capacity for gastric acid generation is kept in check. However, if PPI therapy is abruptly discontinued, large amounts of gastric acid may be generated, which can theoretically aggravate upper GI symptoms (102).

In a study assessing the clinical significance of this physiologic phenomenon, Reimer et al. (103) took persons with no history of GERD or dyspepsia and gave them all PPIs continuously for 8 weeks. At the eighth week mark, these persons were randomized to either placebo or continuing the PPI for an additional 4 weeks; 40% of persons who discontinued the PPI reported dyspepsia in the 4 weeks following discontinuation. In a similarly designed study, Niklasson et al. (104) found that symptoms on PPI withdrawal were significantly correlated with the degree of PPI-induced hypergastrinemia. In a follow-up study where 78 PPI users not having a documented indication were discontinued, nearly two-thirds (51/78) developed upper GI symptoms within 6 months. People who developed upper GI symptoms subsequently underwent endoscopy, where 40% had endoscopic findings consistent with their symptoms, mostly mild esophagitis (105).
One strategy to mitigate against rebound acid hypersecretion-related symptoms would be to taper off PPI use, as opposed to sudden discontinuation. In a study by Inadomi et al. (106) where PPI users were discontinued gradually (1/2 of a standard dose for 2 weeks, then discontinuing), 60% were asymptomatic on no medications or over-the-counter antacids in the year following. Whether a more prolonged taper leads to fewer rebound symptoms is not known, but could be considered for those who develop rebound symptoms with a more rapid taper. In my practice, I will advise persons who wish to discontinue PPIs to take them every other day for 2 weeks, twice per week for 2 weeks, and then to discontinue. I also advise patients who discontinue PPIs to be mindful of rebound symptoms, and not to immediately reintroduce PPIs at the first sign of recurrent symptoms, especially if they occur in the first week after stopping.

SUMMARY
While there is not yet definitive evidence of serious harm associated with PPI use, it remains possible that further studies will be more strongly suggestive of a causal relationship, especially for those associations where biologic plausibility exists. Given the current uncertainty, it behooves the clinician to limit the use of long-term PPIs to those with definite indications, and to actively identify and make attempts to deprescribe PPIs in persons without absolute indications for continued use, or those in whom a reason for ongoing use cannot be determined. When discontinuing PPIs, consideration should be given to step-down strategies, such as using H2RAs, or tapering the dose of PPIs over time. Further, chronic PPI users should be cautioned that upper GI symptoms may recur in the short term, and that the occurrence of these symptoms do not necessarily indicate a need for long-term PPIs, but rather may be a sign of transient reversible gastric acid hypersecretion. Last, health-care systems should aim to develop and evaluate programs to assist and guide physicians and patients through the deprescribing process with the goal of eliminating unnecessary PPI use, and reduce superfluous health-care expenditures.

CONFLICT OF INTEREST
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REFERENCES
77. Masclee GM, Coloma PM, Spaander MC et al. NSAIDs, statins, low-dose aspirin and PPIs, and the risk of oesophageal adenocarcinoma among patients with Barrett’s oesophagus: a population-based case–control study. BMJ Open 2015;5:e006640.
1. Which of the following are clear indications for long-term PPI use
   a. H. pylori infection
   b. Endoscopically proven erosive esophagitis LA class C or higher
   c. EoE with response to PPI therapy
   d. Chronic use of NSAIDs
   e. Symptomatic non-erosive GERD

2. True or False
   a. Patients on long term PPI for >5 years should be screened for osteoporosis and B12 deficiency
   b. Protopathic bias refers to assigning causality to a medication that was started during the prodrome period of the adverse event
   c. Most people with unclear indications for chronic PPI use can be controlled with on-demand PPI therapy rather than daily therapy.
   d. Most patients who discontinue PPI will suffer an acidity rebound that can temporarily worsen symptoms
   e. Many of the studies showing a relationship between PPI’s and a negative outcome have been randomized, prospectively controlled studies
   f. The odds ratios or hazard ratios reported for most PPI-related adverse events are <1.5 and could be accounted for by unmeasured confounding in studies including a large number of subjects
   g. The association described between PPI use and increased C. difficile infection is likely a result of acid suppression allowing C. difficile bacteria to enter the lower GI tract
   h. Discontinuing PPI abruptly is as well tolerated as tapering the dose of PPI over 4 weeks prior to stopping