We must be judicious when prescribing proton-pump inhibitors

"...there is no question that PPIs have had a tremendously positive impact in the treatment of upper GI tract disorders. However, they are currently overused and deleterious effects are becoming apparent."

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Gastrointestinal (GI)-related complaints are amongst the most common reasons people go to the doctor's office, accounting for over 12 million visits in 2000 [101]. Amongst GI diseases, gastroesophageal reflux disease and peptic ulcer disease were the first and fourth-most costly diseases respectively, with gastroesophageal reflux disease alone accounting for over US$9 billion dollars in direct costs in 2000 [1]. Until the late 1980s, the armamentarium of drugs used to treat upper GI symptoms and diseases was limited, with histamine blockers being the most commonly used. Subsequently, in 1989, with the US FDA approval of Prilosec®, the era of proton-pump inhibitors (PPIs) was heralded. Since then, six more formulations have been approved by the FDA, and now the two original PPIs have over-the-counter formulations. With their irreversible inhibition of the sodium/potassium ATPase (proton pump) on the luminal side of the parietal cell, PPIs induce profound acid suppression and achlorhydria; as such, they have been remarkably effective at improving the symptoms of reflux disease, helping to cure peptic ulcer disease and to eradicate *Helicobacter pylori*, affording gastroprotection against antiplatelet effects, and treating dyspepsia, not to mention their therapeutic role in gastrinoma and Barrett's esophagus. Therefore, it should not be surprising that in 2009, PPIs were the third-most commonly prescribed class of drugs, behind only antipsychotics and antidyslipidemics, with total sales reaching nearly $14 billion, and this did not include sales for the three over-the-counter formulations [102]. Their efficacy in treating upper GI disorders has been so great that millions of Americans have been taking PPIs daily for years, despite the fact that most FDA-approved indications are between 2 and 12 weeks in duration. This pattern of PPI use is also, in large part, caused by the class' extraordinary tolerability, with few patients experiencing significant adverse symptoms. However, in the last few years, we have begun to see reports of more and more issues with PPIs, from increasing risks of bone fractures, *Clostridium difficile* infection and bacterial overgrowth to concerns of interactions with antiplatelet agents (clopidogrel) and theoretical concerns regarding long-term achlorhydria. So has this shifted the balance? Should we be more judicious when prescribing PPIs? I would say the answer to these questions is definitely yes; in fact, being judicious with the use of PPIs should have been more strongly emphasized, even before all of the potential complications came to the forefront.

The most recent media attention on PPIs came in May 2010, when the FDA released a consumer warning linking PPIs to an increased risk of fracture of the hip, wrist and spine, based on the review of seven studies [103]. This reignited the debate on overuse of PPIs, but it is important to note that these data were not new. The data have been conflicting, both clinically and pharmacologically. Some studies, most notably the one published in *JAMA* in 2006, do demonstrate an increased risk of hip fracture [2]; the FDA found that six of the seven studies they evaluated supported this finding. However, other studies demonstrate no risk for hip fracture but risk for other fractures [3], some show attenuation of risk over time [4], while others contend that the risk of fracture is seen mostly in those populations already at risk for osteoporosis [5]. If PPIs do indeed increase the risk of fractures, the mechanism by which they do so is unclear. Decreased calcium absorption and increased risk of osteoporosis have been postulated, but these have not been supported by some recent studies [6,7].

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However, despite conflicting evidence that PPIs do increase fracture risk, the studies showing they do should give us reason to pause before indiscriminately prescribing long-term PPIs.

Infectious complications have also been reported with PPIs. Increased rates of *C. difficile* infection have been noted in both out- and in-patient settings [8–10], but whether this is directly related to the potency of acid suppression is still a source of controversy. In addition, studies have demonstrated increased rates of both community- and hospital-acquired pneumonia in the setting of PPI use [11,12]. However, a more recent analysis of patients with community-acquired pneumonia found the risk to only be in the first month of PPI use and not thereafter [13].

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The fact that PPIs so effectively suppress gastric acid may also cause other problems. Normally, the pH of the stomach is essentially sterilizing, killing most bacteria in this highly acidic milieu. By inhibiting the release of hydrochloric acid from the parietal cells, bacteria that would otherwise not survive are able to flourish more distally, thereby changing the small-bowel flora. One study showed that acid suppression increases non-*H. pylori* bacterial concentrations in the stomach, and this can lead to small intestinal bacterial overgrowth (SIBO) [14]. Indeed, a recent paper demonstrated that PPI users are significantly more likely to have SIBO, as assessed by breath testing, than those not using PPIs [15]. Given these findings, along with data on the association of SIBO and irritable bowel syndrome, are we causing an increase in SIBO and irritable bowel syndrome with chronic acid suppression? While much of the increased incidence of irritable bowel syndrome may be caused by heightened awareness and recognition of the disease, we cannot discount the potentially iatrogenic role we are playing by prescribing so much acid suppression in the way of PPIs. Furthermore, with profound acid suppression and therefore achlorhydria, are we also increasing the risk of gastric cancer in the same manner that pernicious anemia-related achlorhydria does? Clearly, this issue is confounded by the role of *H. pylori*, both alone as a carcinogen and by the changes in its pattern and severity with chronic PPI use. Nonetheless, it is definitely worth investigating the potentially carcinogenic role prolonged acid suppression may play, not only in adenocarcinoma, but also in gastric carcinoid via hypergastrinemia and subsequent hyperplasia of enterochromaffin-like cells.

Finally, and perhaps most importantly, in the last 2 years there has been a huge amount of effort dedicated to figuring out the exact role PPIs play in the metabolism and therefore efficacy of the antiplatelet agent, clopidogrel. This issue is worth an article itself, as some studies have demonstrated a deleterious effect of PPIs on clopidogrel activity and/or cardiovascular outcomes, while others have shown no such effect. While the jury is still out on how to use the two medications together (e.g., separating the PPI and clopidogrel in time to minimize competitive inhibition), or if we even should, the FDA issued a statement late last year warning of the interaction; although this view is not necessarily echoed by national GI societies, there are enough data to at least exercise caution. And with clopidogrel so commonly used for cardiovascular disease, this issue will remain important for all gastroenterologists and cardiologists.

There have been many concerns raised over the past few years regarding the potentially dangerous effects of PPIs. While most of the data for each issue are controversial, there are enough concerns to warrant a degree of discretion when prescribing PPIs. When PPIs are indicated, they should be prescribed for a discrete period of time and then the patient should be weaned off the drug. Recent data have demonstrated that the abrupt cessation of PPIs in healthy controls leads to increased acid-related symptoms, so one of the difficulties in getting patients to stop taking PPIs may be that they develop rebound acid hypersecretion upon cessation [16]. To that end, slowly tapering the PPI dosage over several weeks may ameliorate that effect. We should also consider alternative therapies for symptoms that can be treated in other ways. For example, the initial treatment of dyspepsia without alarm symptoms can either be a trial of PPI or a test-and-treat strategy for *H. pylori* [17]. The test-and-treat strategy has a definable end point, while the end point of the trial of PPI is more vague; a short course of PPI should be given, but it is common practice to continue PPIs indefinitely in those who respond. So perhaps we should more strongly emphasize checking for *H. pylori* before moving to empiric PPI in dyspepsia.

In summary, there is no question that PPIs have had a tremendously positive impact in the treatment of upper GI tract disorders. However, they are currently overused and deleterious effects are becoming apparent. While many of

these drawbacks are controversial and have yet to stand the test of prospective trials, they provide enough evidence to warrant using more discretion when considering the initiation of PPIs and, perhaps more importantly, being keen on having an end point of PPI cessation for those in whom it is possible. If we could accomplish these two things, thereby reserving long-term PPIs for those who really need them, we could optimize the risk:benefit ratio.

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