Addicted to acid suppression

I used to think that pharma had their cake and could eat it too as far as proton pump inhibitors (PPIs) were concerned. In the late 70s and early 80s, with the advent of H2 receptor antagonists (H2RAs), pharma companies developed highly effective therapies for healing gastric and duodenal ulcers. Collaboration with academic gastroenterologists allowed the natural history of ulcers to be elucidated and the poor correlation between symptoms and healing of these lesions became clear. Peptic ulcers could be healed by full-dose H2RAs but were likely to recur unless this therapy continued on a maintenance basis. Henceforth, peptic ulcers were considered a chronic disease requiring indefinite therapy.

The concept of ulcers as a chronic disease was displaced by the recognition that infection with *Helicobacter pylori* was the major underlying etiology and that lesions could be cured by combination therapy with potent acid suppression and antibiotics that eradicated this organism. Frankly, pharma companies evinced a rather subtle (sometimes not so subtle) defiance against the concept of an ulcer 'cure' and resisted the potential change in status of ulcers from a chronic disease that required lifelong medicinal acid suppression to one in which a new class of acid-suppressive agents—PPIs—would be needed for a few weeks only. Clearly, the greatest profitability for pharma would lie in demonstrating that the need for maintenance therapy remained.

Then … a medical miracle. What had been described for decades as heartburn became gastroesophageal reflux disease (GERD). Not only had a symptom become a disease, but one that conferred an increased risk of cancer! Hence, GERD became a condition that had to be treated.

Furthermore, many patients with active ulcers who were treated with PPIs to eradicate *H. pylori* developed heartburn symptoms after the cessation of this treatment. To control their GERD symptoms, many ulcer patients needed chronic, indefinite PPI therapy, even though rebound acid hypersecretion is most prominent in patients not infected with *H. pylori*. Hence, although ulcers could indeed be cured, a substantial proportion of patients still required long-term pharmaceutical maintenance therapy—and industry could still have their (self-sustaining) cake.

Most recently, the concept of rebound acid hypersecretion has been revived by a publication from a group based in Copenhagen (Reimer, C. *et al. Gastroenterology* 137, 80–87 [2009]). Reimer and colleagues recognized that rebound acid secretion had been documented after 8 weeks of PPI treatment and could potentially cause acid-related symptoms. They randomly allocated 120 healthy volunteers to 12 weeks of placebo or 8 weeks of esomeprazole 40 mg daily followed by 4 weeks of placebo. Patients completed the Gastrointestinal Symptom Rating Scale on a weekly basis and were questioned about symptoms of heartburn, acid regurgitation or dyspepsia. By the second week after cessation of esomeprazole therapy, 44% of the PPI-treated patients had developed acid-related symptoms compared with 15% of patients who received placebo. These symptoms persisted throughout the 4-week follow-up.

In other words, there is "…evidence that proton pump inhibitor therapy induces symptoms that it is used to treat" (McColl, K. E. & Gillen, D. *Gastroenterology* 137, 20–22 [2009]). The mechanisms of rebound acid hypersecretion are well-recognized and were also seen, to a lesser degree, after treatment with H2RAs. Owing to their potent acid-inhibitory effects, a compensatory increase occurs in levels of circulating gastrin, which activates the cholecystokinin 2 receptor on enterochromaffin-like cells and results in the release of histamine, which acts on the H2 receptor of parietal cells. This altered physiology becomes relevant for a large proportion of patients who do not have GERD, because, as McColl & Gillen comment, "a substantial proportion, if not the majority, of patients now prescribed therapy do not have acid-related symptoms and therefore have no true indication for such therapy".

PPI therapy is often administered empirically—Reimer and colleagues' article reports that up to one-third of patients receive repeat prescriptions without having an obvious indication for maintenance therapy. Rebound acid hypersecretion, rather than a positive effect on symptoms, is likely to account for why withdrawal from long-term PPI treatment is so difficult. Up to 5% of the population of the developed world is receiving PPIs and this market is worth more than US $12 billion—PPIs account for 50% of the most costly prescriptions for gastrointestinal disorders in the US, and for more than 75% of the costs, which equated to US ~$9.5 billion in 2004 (Everhart, J. E. & Ruhl, C. E. *Gastroenterology* 136, 376–386 [2009]).

With so many patients receiving potent acid-suppressive therapy, whether by prescription or over the counter for dyspepsia or unconfirmed esophagitis or ulcers, we need to consider how to wean patients from iatrogenic addiction to acid suppression and the resultant rebound acid hypersecretion, which should be included in the expanding list of potential adverse effects of this (purported and perceived) safe class of therapeutics. So, although PPIs are certainly a major advance for the short-term treatment of peptic ulcers and esophagitis, the acid-suppressive cake should be eaten quickly for most patients while long-term solutions for patients with chronic, nonacid-related dyspepsia and weakened lower esophageal sphincters are sought.

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Competing interests
The author declares no competing interests.