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# Acid peptic diseases: pharmacological approach to treatment

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## Abstract

Acid peptic disorders are the result of distinctive, but overlapping pathogenic mechanisms leading to either excessive acid secretion or diminished mucosal defense. They are common entities present in daily clinical practice that, owing to their chronicity, represent a significant cost to healthcare. Key elements in the success of controlling these entities have been the development of potent and safe drugs based on physiological targets. The histamine-2 receptor antagonists revolutionized the treatment of acid peptic disorders owing to their safety and efficacy profile. The proton-pump inhibitors (PPIs) represent a further therapeutic advance due to more potent inhibition of acid secretion. Ample data from clinical trials and observational experience have confirmed the utility of these agents in the treatment of acid peptic diseases, with differential efficacy and safety characteristics between and within drug classes. Paradigms in their speed and duration of action have underscored the need for new chemical entities that, from a single dose, would provide reliable duration of acid control, particularly at night. Moreover, PPIs reduce, but do not eliminate, the risk of ulcers in patients taking NSAIDs, reflecting untargeted physiopathologic pathways and a breach in the ability to sustain an intragastric pH of more than 4. This review provides an assessment of the current understanding of the physiology of acid production, a discussion of medications targeting gastric acid production and a review of efficacy in specific acid peptic diseases, as well as current challenges and future directions in the treatment of acid-mediated diseases.

### Keywords

acid peptic disease; gastric acid secretion; gastroesophageal reflux disease; histamine-2 receptor antagonist; peptic ulcer disease; proton-pump inhibitor



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Acid peptic diseases result from distinctive but overlapping pathogenic mechanisms that typically involve acid effects on diminished mucosal defense. Conditions such as acid reflux, damage the esophageal mucosa, and also potentially cause laryngeal tissue injury with subsequent development of pulmonary symptoms. A peptic ulcer is histologically defined as a mucosal defect that extends to or beyond the muscularis mucosa, with mucosal damage due to pepsin and gastric acid secretion. Most ulcers occur in the stomach and proximal duodenum while less commonly in the lower esophagus, the distal duodenum or the jejunum.

Acid-related disorders influence the quality of life and productivity of afflicted patients and are common and important causes of morbidity and mortality [1]. Approximately 40% of adults in the USA complain of monthly, 20% of weekly, and approximately 7% of daily heartburn [2], making gastroesophageal reflux disease (GERD) one the most common gastrointestinal (GI) disorders with resultant costs of more than US$10 billion per year [3]. Despite a declining incidence owing to increased application of eradication therapy against *Helicobacter pylori*, peptic ulcer disease (PUD) afflicts several million people in the USA every year [4].

In broad terms, the development of potent, and safe drugs based on physiologic targets has been an impressive success in modern therapeutics. A key element of this success has been the control of gastric acid. Peptic acid diseases arise from distinctive but overlapping pathogenic mechanisms, but ultimately have a common mechanism of tissue injury from acid. Gastric hydrochloric acid secretion is modulated by neural and hormonal stimulation of receptors on the basolateral membrane, as well as by activation of enzymes located on the surface of parietal cells. Modern therapy is aimed at these physiological targets.

Goals of therapy include relief of symptoms, enhancement of ulcer healing in the affected mucosa (esophagus, stomach and duodenum) and prevention of recurrence. Milestones in the treatment of these diseases have included:

- The discovery of the histamine H2-receptor and its functional antagonists
- Identification of the $H^+$ $K^+$-adenosine triphosphatase ($H^+K^+$-ATPase) enzyme and the development of proton-pump inhibitors (PPIs)
- Confirmation of *H. pylori* as a peptic ulcer causative agent with the subsequent development of effective antibiotic eradication regimens

This review will provide a pharmacological approach to common acid peptic disorders based on physiological targets in acid secretion. Briefly, the mucosal protective agents are also discussed as they play some role in treatment strategies for these conditions.

## Physiology of acid secretion

The stomach consists of an epithelium made up of pits and glands. The two primary functional zones are the oxyntic gland area, representing approximately 80% of the organ, and the pyloric gland area representing the remaining 20% [5]. Parietal cells, which predominate in the oxyntic glands, secrete hydrochloric acid and intrinsic factor. They are located in the lower two-thirds of the oxyntic glands and are largely limited to the fundic region of the stomach. Chief cells, located at the base of the oxyntic glands, are responsible for secreting the digestive enzyme precursor pepsinogen. Neuroendocrine cells containing hormonal and paracrine signaling agents that regulate the activity of the parietal cell reside within the glands. These include D cells, enterochromaffin-like (ECL) cells, A-like cells and enterochromaffin (EC) cells [6].

## Regulation of acid secretion

Parietal cell acid secretion is initiated by a variety of factors related to food ingestion. Regulation is via central, peripheral and cellular mechanisms. Acid is generated by the carbonic anhydrase-mediated catalysis of $CO_2$ and $H_2O$ to form $H^+$ and $HCO_3^-$. $H^+$ ions are then exchanged for $K^+$ by the $H^+K^+$-ATPase pump and later coupled with $CL^-$ ions entering the parietal cell from the blood in exchange for $HCO_3^-$.

Most of the vagal fibers supplying the stomach are afferent [5,7] and relay information to the brain regarding mechanical and chemical changes in the stomach [8]. The efferent fibers are preganglionic neurons that do not directly innervate the parietal cells, but rather synapse with postganglionic neurons in the wall of the stomach. These neurons contain neurotransmitters, such as acetylcholine, gastrin-releasing peptide (GRP), vasoactive intestinal peptide (VIP), pituitary adenylate cyclase-activating polypeptide (PACAP), nitric oxide and substance P [9]. Through these messengers, postganglionic neurons are able to regulate acid secretion directly by influencing the parietal cell, or indirectly by modulating the secretion of hormonal and paracrine ligands. Sympathetic receptors of the stomach consist of unmyelinated nerve endings located within the smooth muscle layer. These detect chemical stimuli more than mechanical stimulation and play a role in conveying pain sensation associated with inflammatory states, such as gastritis.

The principal stimulants for acid secretion are histamine, gastrin and acetylcholine released from postganglionic enteric neurons [5]. These raise intracellular levels of adenosine 3′,5′,-cyclic monophosphate (cAMP), inositol triphosphate (IP3), diacylglycerol and calcium [5,10]. This sequence of events induce $H^+K^+$-ATPase rich tubulovesicles to fuse into the apical plasma membrane allowing the $H^+K^+$-ATPase to secrete protons directly into the lumen of the canaliculus of the parietal cell and then into the lumen of the gastric gland.

**Histamine—**Histamine is produced in ECL cells located in the oxyntic mucosa. It serves as the major paracrine stimulator of acid secretion. Histamine is produced in ECL cells by decarboxylation of L-histidine by histidine decarboxylase (HDC). In the gut, H2 receptors on the parietal cell increase adenylate cyclase activity and generate cAMP [11]. HDC promoter activity is upregulated by gastrin, *H. pylori* and PACAP. Targeted gene disruption of HDC and the H2 receptor demonstrate the key role of gastric acid secretion mediated by hormones such as gastrin or PACAP. HDC-knockout mice produce little or no histamine, resulting in impaired acid secretion and a failure to respond to gastrin [12]. However, functional antagonists of the H2 receptor only partially inhibits acid secretion stimulated by cholinergic agents. H2 receptors are also localized in smooth muscle and cardiac myocytes, which may explain why certain cardiac arrhythmias have been observed with rapid infusion of intravenous H2 antagonists. H3 agonists stimulate acid secretion indirectly by inhibition of somatostatin-induced histamine release [13–15]. There are no approved drugs specifically targeting the H3 receptor.

**Gastrin—**Gastrin, the main stimulant of acid secretion during meal stimulation [5], is produced in response to luminal amino acids derived from dietary intake. Initially, gastrin is synthesized as a precursor molecule that is cleaved post-translationally into acid-stimulatory peptides, of which gastrin-17 and gastrin-34 are the most abundant, and N-terminal fragments, of which progastrin 1–35 and progastrin 1–19 dominate [16]. Gastrin is the most potent endogenous stimulant for gastric acid secretion by favoring synthesis and release of histamine from ECL cells.

Gastrin resembles cholecystokinin (CCK), as it possesses an identical C-terminal pentapeptide sequence. Two main classes of gastrin/CCK receptors have been characterized: CCK-1 and CCK-2. CCK-1 receptors are specific for CCK whereas CCK-2 receptors

recognize both CCK and gastrin. When CCK-2 receptors become stimulated in parietal and ECL cells, they lead to activation of phospholipase C and release of intracellular calcium [17–19]. Gastrin is thought to regulate the secretion of histamine by increasing the release of stored histamine and by increasing the activity and gene transcription of HDC [20]. Gastrin also has a trophic effect on the oxyntic mucosa, particularly on ECL cells, and it can induce hyperplasia, hypertrophia and carcinoids in rats [6]. A number of neoplasms are gastrin sensitive, including gastric carcinoids and cancers of the stomach, colon, pancreas and lung [21]. This observation raised concerns of carcinogenesis in humans owing to long-term PPI-induced hypergastrinemia. However, prolonged retrospective observation in humans has not detected an increased incidence of cancer [22,23].

In the stomach, gastrin mediates its effects primarily through the CCK-2 receptor. The stimulatory pathways for gastrin release are central and peripheral. Neural pathways to the G cells are both inhibitory and stimulatory. Peripheral pathways to the G cells are initiated by the presence of food in the stomach as signaled by mechanical distention, pH and the presence of amines and specific amino acids. When the pH of the gastric lumen falls below 3, a negative feedback mechanism involving calcitonin-gene related peptide [24–26] inhibits gastrin release, while hydrogen ions may also protonate amino acids and reduce their uptake by the G cells. Luminal pH also activates sensory nerve cells, enhancing somatostatin release that acts as a paracrine agent to suppress gastrin secretion [27].

**Acetylcholine—**Acetylcholine from parasympathetic vagal efferents modulates basal acid secretion. It is released from postganglionic neurons of the enteric nervous system and directly stimulates acid secretion by binding to muscarinic (M3) receptors on parietal cells. Acetylcholine may also stimulate acid secretion indirectly by inhibiting the release of somatostatin through activation of M2 and M4 receptors on D cells [5]. The importance of acetylcholine in the PUDs has made it a target of anticholinergic drugs. However, the doses usually required to suppress acid secretion are commonly associated with the development of undesirable side effects, such as dry mouth, blurred vision and urinary retention.

**Somatostatin—**Somatostatin is the major physiological inhibitor of acid secretion [5]. It is released in two forms. Somatostatin 14 is found mainly in the stomach, pancreas and enteric neurons, while somatostatin 28 is the major form present in the small intestine. Somatostatin exerts tonic inhibitory effects on parietal cells, however, the major effects are accomplished by the inhibition of histamine release and gastrin release from ECL cells and G cells [28–31]. The secretion of somatostatin is increased by gastric acid and by gastrin. It is suppressed by cholinergic activation and increased by vasoactive intestinal peptide activation. The somatostatin analog octreotide has a theoretic potential in the treatment of acute ulcer bleeding, but its efficacy in an era of modern acid suppression agents has not been definitely demonstrated [32–34].

**Other regulators of acid secretion—**Ghrelin has been studied as a stimulant of acid secretion involving the vagus nerve and histamine release [35,36]. Other neurotransmitters, such as the neuropeptide GRP have been linked with meal-stimulated acid secretion. GRP mediates its effects by gastrin release and it may also be an important neurotransmitter in the vagal–cholinergic pathway, as demonstrated by the GRP antagonist BIM26226, which blocks vagally mediated acid secretion in humans in similar ways to atropine [37]. CCK may also function as a physiologic inhibitor induced by the presence of nutrients in the intestine [38,39]. Other inhibitors of acid secretion that stimulate somatostatin release include glucagon-like peptide, CCK, VIP, leptin, amylin and EGF.

### $H^+K^+$-ATPase (the proton pump)

The $H^+K^+$-ATPase, also commonly called the proton pump, is the molecular engine of gastric acid secretion and is solely responsible for the secretion of hydrogen ions into the lumen of the gastric glands and stomach. This represents the last step in the secretion of gastric acid. The proton pump carries out the exchange of luminal $K^+$ for cytoplasmic $H^+$ through ATP hydrolysis. It is composed of two subunits: an α-subunit and a glycosylated β-subunit. The α-subunit carries out the catalytic and transport functions of the enzyme, reacts with ATP, defines cation binding properties, hydrolyzes ATP and is the site for binding of PPIs [40]. The smaller glycosylated β-subunit protects the enzyme from degradation and is essential for the structural and functional stability of the ATPase [13]. Moreover, it appears to play a key role in targeting of the pump to the apical membrane, in the development of the oxyntic mucosa and in recycling the pump from the ‘active’ secretory canaliculi back to the tubulovesicular membranes when the cell reverts to a ‘resting’ state [41]. Interestingly, each subunit is critical for enzyme activity since deletion of either the α-subunit or the β-subunit in mice causes achlorhydria [42].

The $H^+K^+$-ATPase is an enzyme found only on secretory membranes of parietal cells that, in the resting unstimulated state, are contained in abundant membranous structures rich in $H^+K^+$-ATPase in the form of microtubules, vesicles and tubulovesicles. When gastric HCl secretion is stimulated there is a morphological transformation leading to migration of the tubulovesicles into the apical plasma membrane, allowing the $H^+K^+$-ATPase to secrete protons directly into the lumen of the gastric gland. Upon cessation of secretion, the pumps are retrieved from the apical membrane and the tubulovesicular compartment is re-established.

## Drugs modulating gastric acid

### Antacids

Histamine 2 antagonists and PPIs have largely replaced antacids as primary treatment for most acid-peptic disorders; nevertheless, there is still a role for their use as they are inexpensive, readily available, and safe in most populations. Antacids work nearly instantaneously and find utility for rapid relief of mild or sporadic symptoms. The primary effect of antacids on the stomach is due to partial neutralization of gastric hydrochloric acid and inhibition of the proteolytic enzyme pepsin [43]. Neutralization of acid in the gut lumen bypasses the need for systemic absorption of the drug. They are all administered orally and their potency is usually measured by the amount of acid neutralized by a given dose of the antacid. The effective time for antacids to reduce stomach acidity is relatively short on an empty stomach, but can be prolonged to 1–3 h if taken with food.

Commonly used antacids contain sodium bicarbonate, calcium carbonate, magnesium hydroxide and aluminum hydroxide. Usual formulations are liquid suspensions or solid tablets. Sodium bicarbonate found initial common use as an antacid and is still employed occasionally as a self-prescribed regimen of ‘baking soda’ mixed in water, or in combination products containing aspirin. However, the soluble nature of sodium bicarbonate has made it less desirable, as larger doses can lead to systemic alkalosis and high sodium load, which can be problematic in patients with systolic cardiac dysfunction or renal insufficiency. Most commonly used antacids contain less soluble agents, given alone or in combination. For example, calcium carbonate is sparingly soluble. Reaction with HCl generates soluble calcium chloride, which is converted back to calcium carbonate in the alkaline conditions of the small intestine. This precipitates out into the stool, decreasing absorption. Other commonly used agents are the insoluble antacids aluminum hydroxide and magnesium hydroxide. Aluminum- and calcium-containing products can cause constipation. To

counteract this, these agents are often combined with magnesium hydroxide, which, when administered alone, can cause diarrhea and loose stools.

Compliance has been another factor affecting efficacy of antacids and it appears to be limited by the need for frequent dosing and the poor correlation between symptomatic relief and ulcer healing [44]. Antacids are not currently used for the treatment of PUD and have modest efficacy in healing peptic ulcers. Meta-analysis suggests lack of effectiveness in nonulcer dyspepsia [45]. This is not surprising in light of the limited number of studies in an era of potent acid-suppressing drugs and the weak link between acidity and symptoms in nonulcer dyspepsia [46]. By contrast, antacids demonstrate a modest (10%) improvement in GERD symptoms compared with placebo [47] Although antacids are effective for stress-ulcer prophylaxis in critically ill patients, the present role for these agents resides primarily in the treatment of mild symptomatic reflux and dyspepsia [48].

Adverse events associated with antacids are dose-related. Large doses of calcium-containing antacids can cause the milk-alkali syndrome, which consists of hypercalcemia, renal insufficiency and metabolic alkalosis [49]. Magnesium-containing antacids can cause diarrhea if administered alone and may lead to hypermagnesemia in patients with renal insufficiency. Aluminum-containing antacids can cause encephalology and osteomalacia in end-stage renal patients and calcium carbonate is the preferred antacid in this population [50]. Although specific interactions with medications are unusual, all antacids can produce drug interactions by changing gastric or urinary pH by altering rates of absorption [43], bioavailability, renal elimination and drug dissolution, or by reducing gastric acid hydrolysis of drugs.

## H2-receptor antagonists

Functional antagonists to the H2 receptor were described in 1972 [51]. Since then, this class of agents revolutionized the treatment of PUD and their primacy in the treatment of acid-related diseases has been surpassed only by the development of the PPIs. The four widely available H2-receptor antagonists (H2RAs) are cimetidine, ranitidine, famotidine and nizatidine. All act on the H2 receptor (Table 1). The H2RAs are reversible structural analogs of histamine that cause a decrease in the tonic activation rate of the receptor, thus, these agents act as inverse agonists with a functional antagonism of histamine activity [52,53].

Histamine primarily mediates the basal rate of acid release during nonfeeding periods. This is of particular importance during the nocturnal periods of fasting, which is the rational for the use of H2RA dosing at bedtime. Models based upon 24 h pH monitoring and clinical trials data have demonstrated that ulcer healing depends on the amount of acid suppression as well as the duration of the 24 h cycle with reduced acidity, with a pH of over 3 for duodenal ulcer and a pH over 4 for GERD [54,55].

Cimetidine, ranitidine, famotidine and nizatidine contain a heterocyclic ring and generally have similar structural and pharmacokinetic characteristics. H2RAs are well absorbed in the small intestine after oral dosing, achieving peak concentrations within 1–3 h. This rate may be influenced by concomitant use of antacid therapy but rarely by food ingestion. All agents have linear pharmacokinetics and are eliminated primarily by renal mechanisms, with 30–60% of the drug being excreted unchanged into the urine. Dose adjustments are needed for patients with renal impairment, but not in those with liver disease.

The experience with H2RAs is extensive with a few common dose-dependent adverse events observed in approximately 1.5% of treated patients [2,56]. The H2RAs are often administered once a day prior to bedtime to maximally impact nocturnal basal acid secretion. However, the added benefit of the addition of night time H2RA to an existing PPI

regimen, even in those with known nocturnal acid breakthrough, is debatable. [57]. Effects on acid secretion tend to decline with time. This probably represents an exaggerated first-dose response rather than typical tolerance [58]. Use of a H2RA causes decreased H2-receptor degradation [59], which may clinically manifest as rebound acid secretion upon drug cessation. These characteristics, coupled with the rapid onset of action relative to the PPIs, make the H2RAs better suited to a symptom-driven on-demand use rather than as primary acid controllers.

The H2RAs have an excellent safety profile that supports common use as over-the-counter medications. Cimetidine has a mild antiandrogenic effect, which has been the cause of gynecomastia and impotence. Hematological abnormalities include myelosuppression, thrombocytopenia, anemia and neutropenia. CNS symptoms include confusion, restlessness, headaches and mental status change. These are more common in elderly patients in the intensive care unit (ICU) who have hepatic and renal complications. Rarely observed cardiac effects are seen following rapid intravenous administration or high-dose therapy, particularly in those with limited physiologic reserve. There are potential drug interactions with cimetidine due to inhibition of cytochrome P450 (CYP) enzymes, particularly CYP3A4 and 2D6. Cimetidine also inhibits the tubular secretion of some drugs, and it is by this mechanism that the drug can also modestly increase the serum creatinine.

Evidence supports the effectiveness of H2RA in acid peptic disorders and there is good evidence that on-demand use relieves heartburn symptoms, although it is not effective in controlling erosive esophagitis [60]. Over-the-counter H2RAs doses (ranitidine 75 mg, famotidine 10 mg), are less than those listed in the prescription product insert, however, at these doses they are effective in reducing overnight gastric acidity for 12 h [61], as well as blunting the food-stimulated gastric response [62,63]. They are also effective in the treatment of symptomatic GERD [47].

Histamine receptor antagonists have modest efficacy in nonulcer dyspepsia [45], however, they are not as effective as PPIs [64]. H2RAs are superior to placebo, but inferior to PPIs for the treatment of esophageal reflux disease [64–66]. Similarly, PPIs are superior to H2RAs in the prevention of rebleeding of an acute peptic ulcer [67], and in ulcer symptoms and healing [68,69]. In the prevention of NSAID-induced injury, standard doses of H2RAs are effective at reducing the risk of duodenal but not gastric ulcers, while double-dose H2RAs were effective at reducing the risk of endoscopically visualized duodenal and gastric ulcers [70].

## Proton pump inhibitors

As the gastric $H^+K^+$-ATPase was identified as the common pathway for acid production [71], the inhibition of this step in gastric acid production has revolutionized the treatment of diseases of the GI tract. The PPIs are the most potent inhibitors of gastric acid secretion. Five widely used PPIs (omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole) and the recently approved dexlansoprazole, are orally available (Table 2). Whereas intravenous formulations of pantoprazole, lansoprazole and esomeprazole are available in the USA, intravenous omeprazole is used in other countries. PPIs are weak bases that act as prodrugs and need an acidic environment in order to inhibit the $H^+K^+$-ATPase [10]. All these compounds share a common structure consisting of substituted pyridylmethylsulfinyl benzimidazoles that varies in terms of the substitutions on either the pyridine or the benzimidazole rings [58]. As a result of their acid dissociation constant (pKa) levels, they accumulate in the secretory canaliculus of the parietal cell, achieving higher concentrations here when compared with plasma. The PPI becomes protonated and converted into the active sulfenamide species, which forms disulfide bonds with cysteine residues in the α-subunit of the $H^+K^+$-ATPase. This results in duration of action that exceeds

plasma half-life, as well as an inhibitory mechanism that is independent of histamine, acetylcholine, or gastrin stimulus for acid secretion [40,72]. By contrast, with H2RAs, PPIs also decrease pepsin secretion [73], which serves to reduce mucosal damage.

In addition, in contrast to the H2RAs, in which optimal dosing is at night, morning dosing of PPIs is associated with significantly improved acid suppression [74,75]. PPIs should be administered before breakfast as the amount of $H^+K^+$-ATPase present in the parietal cells is greatest after a prolonged fast and eating will recruit $H^+K^+$-ATPase to become active and susceptible to drug action. The effects of the PPIs increase with repeated administration and, generally by the third day, a steady state occurs where the amount of pumps that remain inhibited over 2 h reaches approximately 70%. Moreover, acid suppression improves progressively as the recruitment of the enzyme increases. Consequently, the occasional use of a PPI taken on an 'as needed' basis does not reliably provide adequate acid inhibition and does not produce a consistent or satisfactory clinical response [72,76].

Proton-pump inhibitors undergo metabolism via hepatic CYP2C19. Of the PPIs, rabeprazole is unique as only 15–20% of its metabolism involves the CYP system. There is differential metabolism between individuals due to pharmacogenetic variation. Poor metabolizers constitute approximately 2–6% of Caucasian and 15–20% of Asian populations and they tend to have higher plasma drug levels, more profound acid inhibition and higher healing rates in PPI-containing *H. pylori* regimens. However, pharmacogenetic testing of patients has not been demonstrated to routinely improve outcomes and is not advocated [77].

All PPIs have an excellent safety profile in both clinical trials and postmarketing pharmacovigilance [78]. The three main concerns regarding the long-term safety of the class include prolonged hypergastrinemia, the possible association of PPIs with gastric atrophy and chronic hypochlorhydria [76]. Gastrin is a proliferative hormone with a theoretic potential to promote cancer. The original package insert for PPIs contained a black box warning about this potential. This warning was removed as it became clear that the drugs do not appear to be mutagenic, nor are they associated with increased rates of colon cancer or gastric carcinoids [22]. Possible associations with hip fractures [79], renal complications [80] and community-acquired pneumonia [46,81] have also been demonstrated. Systematic review suggests increased enteric infections (including *Clostridium difficile*) associated with acid suppression [82]. While there is biologic plausibility to such an observation, the data are heterogeneous and a direct causal relationship has not been established.

Suppression of gastric acid by PPIs interrupts negative-feedback mechanisms by which gastrin secretion is regulated, since high levels of gastric acid normally inhibit gastrin secretion, prolonged PPI treatment leads to hypergastrinemia. The phenomenon described as rebound acid hypersecretion (RAHS) after administration of a PPI was first demonstrated in animals treated with omeprazole [83], similarly, this has also been demonstrated in humans who used PPI [84,85]. Gastrin exerts a trophic effect on the ECL cells and PPIs may induce hyperplasia or even neoplasia of ECL cells, a possible mechanism that could explain RAHS after cessation of proton-pump inhibition. Nevertheless, despite confirmed strong associations between elevated serum gastrin concentration and ECL cell hyperplasia, studies have not found significant evidence that the hyperplasia observed in patients on PPI therapy progresses to the higher grades of hyperplasia that may be the precursor to gastric ECL cell tumors [86–88]. However, the clinical importance of this factor translates into a potential worsening of GERD symptoms, which seems to be more important in *H. pylori*-negative patients [89]. This clinical consideration may interfere with the treatment duration of patients with GERD or dyspepsia, exposing these patients to prolonged use of PPIs and potential long-term side effects. Nevertheless, issues such as this have been documented in a limited fashion through the literature and more studies are required in this area.

Proton-pump inhibitors can decrease the bioavailability of drugs with acid-dependent absorption. These include the HIV-protease inhibitor atazanavir, as well ampicillin, iron and digoxin. Omeprazole is an inhibitor of CYP2C19, which can increase the levels of substrates such as diazepam and phenytoin. Omeprazole, but not pantoprazole or esomeprazole [90,91], has been noted to decrease the platelet inhibitory effect of clopidogrel, however, demonstration of adverse clinical outcomes based on this pharmacodynamic interaction are lacking. PPIs should not be administered concomitantly with H2-antagonists, prostaglandins or other antisecretory agents owing to the marked reduction in their acid inhibitory effects when administered simultaneously; however, sufficient time interval between administration of the H2 antagonist and the PPI is recommended when there is a need of concomitant therapies.

## Mucosal protective agents

### Sucralfate

An aluminum salt of sulfated sucrose and aluminum hydroxide are the basic compounds that form sucralfate. It is a nonabsorbable medication that binds to gastric mucosa and ulcerated tissue. These properties favor healing and provide cytoprotective effects [92]. When exposed to gastric acid the sulfate ions bind to proteins in the damaged gastric tissue of ulcer craters and stimulate angiogenesis, delivery of growth factors and formation of granulation tissue [93]. This binding is favored by a low pH and is the rationale for use 30–60 min before meals. The drug is excreted in feces and only a minor increase on serum and urinary aluminum has been reported with its use, owing to this concern, sucralfate is best avoided in patients with kidney failure

Sucralfate has similar efficacy in healing of duodenal ulcer and gastric ulcers when compared with H2RAs [92]. The primary utility is in the prophylaxis of stress ulceration in critically ill patients. Clinical trial data are sparse, however, sucralfate appears to have similar efficacy to H2RAs for the prevention of critical care stress ulceration and hemorrhage. Sucralfate may offer an advantage over H2RAs and possibly PPIs for the prophylaxis of stress-related mucosal injury on the basis of maintaining a lower intragastric pH and conserving the sterilizing effects of an acidic stomach. On this basis, it has been reported to have a lower incidence of nosocomial pneumonia in comparison with antacids and H2RAs [94]. However, studies have demonstrated no significant differences in the incidence of nosocomial pneumonia in critically ill patients when treated with sucralfate versus acid-suppression therapy [94–96].

### Bismuth

The commonly used salt of salicylic acid, bismuth salicylate has antacid properties. Bismuth suppresses *H. pylori* and has been approved by the US FDA for use in combination with other agents for its eradication. Other actions that may promote ulcer healing include inhibition of pepsin activity, increase in mucosal prostaglandin production and mucus and bicarbonate secretion. It is largely unabsorbed and is excreted in feces. In the colon it reacts with hydrogen sulfide and forms bismuth sulfide, which blackens the stools. In has modest efficacy in nonulcer dyspepsia [45], and is presently used in *H. pylori* regimens.

### Prostaglandins analogs

The theoretical basis for prostaglandin therapy is to counteract the systemic effects of NSAIDs and enhance epithelial cell growth and repair [97]. Early work led to the development of misoprostol, arbaprostil, enprostil and rioprostil. Of these, analog approved by misoprostol is the only prostaglandin $E_2$ the FDA for the prevention of NSAID-related ulcers and is designed to help overcome the NSAID-induced deficiency of prostaglandins in

the gastric mucosa It is usually administered by mouth with a good absorption achieving a peak plasma concentration in 30 min and a half life of 1.5 h. The drug has no effect in the CYP system and its metabolites are excreted in the urine. Misoprostol is the only prostaglandin analog that has been demonstrated to reduce serious gastroenterologic complications from NSAID therapy [98], and has been found to be superior to H2RAs for prevention of gastric, but not duodenal, ulcers [99]. However, misoprostol only represents 2% of medical co-therapy prescriptions for NSAID users owing to common side effects of abdominal cramps and diarrhea causing discontinuation of therapy and adherence issues associated with multiple daily doses [100].

## Acid-related diseases

Acid-related diseases involve a variety of disorders that can affect the esophagus, stomach and duodenum. The prevalence of chronic acid-related disorders in the USA is approximately 2.3%, with GERD representing more than half of the disease burden [101]. Others have reported a prevalence of one or more upper GI symptoms in up to 44.9% of patients [102]. GERD stands out as one of the most common GI disorders, afflicting more that 60 million Americans, with up to 20% of the population having symptoms at least twice a week [103]. PUD is another GI disease mediated by acid, with 500,000 cases in the USA each year, most of which occur in patients between the ages of 25 and 64 years [104]. These conditions diminish the quality of life and increase the cost of care for patients [105–107], and eventually may progress to malignant conditions such as adenocarcinoma.

### Gastroesophageal reflux disease

Gastroesophageal reflux disease is the exposure of esophageal mucosa to acidic gastric contents, as well as pepsin and bile acids. Reflux is due to anatomical and functional interactions involving the stomach, gastroesophageal junction, lower esophageal sphincter and nervous system. Reflux leads to altered clearance and protective mechanisms of the esophagus. GERD is a chronic entity that can result in esophageal mucosal injury, which is usually erosive esophagitis. However, it is estimated that approximately 50–70% of GERD patients never develop esophagitis, and such patients are referred to as having nonerosive gastroesophageal reflux disease (NERD). Patients with GERD usually complain of heartburn and acid regurgitation as the classic symptoms. When both of these are present, the diagnosis can be made clinically with 90% accuracy [108]. Nevertheless, the frequency and severity of heartburn does not predict the degree of esophageal damage [109]. Other possible presentations of GERD with an uncertain diagnostic yield include chest pain, cough and other symptoms such as dysphagia.

Taking into consideration the various pathogenic mechanisms, the treatment of this entity has focused on limiting the exposure of acid and decreasing the amount of acid produced by the stomach. GERD is a chronic condition that requires long-term treatment. More than 80% of patients require acid-suppressive medications to control their symptoms. For these reasons, consensus opinion suggests that the initial GERD treatment requires a symptom-based, rather than a pathogenesis-based, approach [110]. PPIs have shown superior results when compared with H2RAs for treating heartburn and healing erosive esophagitis [64,65,111], and are considered the drug of choice for an empirical therapeutic trial [112], despite the fact that a response to such strategy does not fully establish the diagnosis of GERD.

Acid suppression represents the mainstay of GERD therapy. Antacids are primarily used as patient-initiated self treatment, or as a symptomatic breakthrough adjunct in PPI or H2RA regimens. H2RAs are available as over-the-counter formulations providing an inexpensive initial management. Moreover, symptomatic relief can be expected in up to 60% of patients

and healing rates can be achieved in approximately 50% of patients treated with H2RAs, whereas PPIs rates are 83 and 78%, respectively, making PPIs more effective for the empirical treatment of heartburn [65,113]. In this context, the treatment of endoscopically confirmed symptomatic GERD with PPIs demonstrates better efficacy in obtaining clinical remission and healing rates [114].

The end point of symptom relief can be more difficult to obtain when compared with achieving mucosal healing in GERD and second doses of a PPI or longer treatment duration may be needed in these cases. NERD trials using omeprazole 20 mg have shown less symptomatic relief in the majority of NERD patients in comparison with rates of relief of approximately 80% on those with erosive GERD [115]. When treated with omeprazole 20 mg/day, only 46–57% of NERD patients demonstrated remission of symptoms of heartburn after 4 weeks of therapy [116]. In addition, using lansoprazole 15 or 30 mg/day provided symptomatic relief in only 45 and 39% of NERD patients respectively [117], thus, extending the duration of therapy or increasing the doses in patients classified as ‘nonresponders’ will not necessarily improve treatment efficacy. This suggests that at least some symptoms in NERD have a nonacid etiology

The superiority of PPIs in preventing relapse is best achieved with full-dose rather than half-dose [5,118]; however, relapse of symptoms may occur in up to 70–80% of both esophagitis and NERD patients, particularly in those with more severe cases of esophagitis [64,119,120]. Consequently, maintenance treatment is often required for symptom control resulting in high medication costs for GERD patients.

Occasionally PPI given twice daily does not suppress gastric acid secretion sufficiently overnight. This event, known as nocturnal gastric acid breakthrough (NAB), arbitrarily defined as intragastric pH of less than 4 for more than 1 continuous hour overnight, occurs in approximately 70% of both normal volunteers and patients with gastroesophageal reflux disease [121]. In addition, esophageal acid exposure occurs in 30–50% of patients during the nocturnal gastric acid breakthrough period and it might be sufficient to produce nocturnal symptoms and mucosal injury in patients with severe erosive esophagitis, Barrett’s esophagus and extraesophageal manifestations of GERD [122]. This pharmacologic phenomenon has been reported with similar frequency with omeprazole, lansoprazole, rabeprazole and pantoprazole, and was demonstrated in both healthy subjects and patients with GERD [123]. Moreover, in patients taking a PPI once-daily before breakfast, NAB occurs in the early evening, in patients taking their PPI before dinner the phenomenon occurs 6–7 h after this dose [124]. Several strategies have been employed in an attempt to control night time acids including once-at-night administration of a PPI, twice-a-day use of PPI, or adding H2RAs to a PPI regimen [5]. However, evidence to support any particular one of these approaches is lacking [57,125,126], and patients with chronic conditions, such as systemic sclerosis, may experience esophageal acid exposure despite high-dose acid suppression with omeprazole or additional ranitidine at night time without improvement in NAB, GERD or quality of life [127].

Furthermore, the clinical importance of NAB in healthy volunteers and patients with mild GERD is more controversial. In a report, the association of esophageal pH with nocturnal acid breakthrough was studied in 17 patients who had symptomatic NAB. Each participant received various regimens of acid-suppressive medications: increasing the PPI to twice a day, having the PPI administered early in the morning or just before going to bed, adding an H2RA at night, or increasing the PPI to three-times a day. The investigators found that the treatment regimens resulted in NAB elimination of 9–41% and that the vast majority of these patients, 60% at least, did not have their nocturnal acid breakthrough controlled by any of these methods, concluding that nocturnal acid breakthrough is an isolated gastric

phenomenon and esophageal acid suppression and symptom control are not dependent on the degree of nocturnal acid elimination [128]. These data suggest that there appears to be a disconnect between NAB and symptom control. NAB has been defined as an intragastric phenomenon not necessarily associated with nocturnal intraesophageal acid exposure or nocturnal GERD symptoms [129]. It seems, therefore, that the control of nocturnal acidity may not yield to any particular strategy, and also that total elimination of NAB is not necessarily associated with resolution of all symptomatic reflux disease.

Formulations, such as immediate-release omeprazole (IR-OME), used at night time have shown promising results for a rapid and better control of night time acid production. Using the idea that a rapid alkalinization of gastric contents by the sodium bicarbonate portion of this formulation will lead to rapid activation of proton pumps, which will be better inhibited by the peak plasma concentrations achieved by the omeprazole moiety, randomized controlled clinical trials showed that this novel formulation provides better control of night time pH compared with delayed- release PPIs [130]. Moreover, when compared with pantoprazole, the median percentage time of intragastric pH of more than 4 at night time was superior for IR-OME (55%) versus pantoprazole (27%) [130].

Barrett's esophagus is a significant complication that affects up to 15% of GERD patients leading to adenocarcinoma of the esophagus at a rate of approximately 0.5% per year [131]. In patients with Barrett's esophagus, acid suppression becomes important as it may play a role in retarding the progression of dysplasia when compared with H2RAs or no therapy [132]. These pharmacological agents, when used twice daily or at higher doses [133], have been found to induce the formation of esophageal squamous islands in approximately 50–80% of patients after a long and aggressive therapy; unfortunately, there is no conclusive evidence that they lead to a regression of Barrett's esophagus and there is not prospective evidence that such therapy prevents cancer [134,135].

Extraesophageal manifestations of GERD refer to patients with symptoms not typical of this disease. These include symptoms, such as hoarseness, sore throat, asthma, chronic cough or noncardiac chest pain [136]. GERD is the cause of chronic cough in 10–40% of cases, as demonstrated by pH monitoring, barium x-ray and endoscopy and therapeutic response to acid suppression [137,138]. Viewing the evidence across clinical trials, response to empiric PPIs is inconsistent [139], and, regardless of how the diagnosis of GERD-induced cough is made, no clear guidelines exist regarding medical therapy [140]. Similarly, Cochrane reviews revealed that while subsets of asthmatic [141] and laryngitis [142] patients improved with treatment, such patients cannot be easily identified and overall treatment with GERD therapy is not associated with statistically significant improvements in outcome. Whether PPIs are effective or not in extraesophageal manifestations of GERD remains an important area of controversy and uncertainty. The relationship between *H. pylori* and GERD remains unclear [143]. Evidence suggests that eradication of *H. pylori* has no influence on relapse of GERD or esophageal acid exposure. Testing for and eradication of *H. pylori* has not been shown to be advantageous for patients with GERD [143]. In fact, eradication of *H. pylori* may be associated with mild worsening of GERD symptoms in patients with pan-gastritis [144–146].

## Peptic ulcer disease

Peptic ulcer disease remains a relatively common disorder despite its declining incidence [4]. Antisecretory therapy is the keystone of therapy in patients with PUD. Indeed, with the introduction of PPIs, the healing and cure rates have improved dramatically. Eradication of *H. pylori* infection has revolutionized the approach to treatment of PUD and is now the mainstay of treatment for this disease. This has resulted in high ulcer healing rates and decreased recurrence rates, especially for individuals with a duodenal ulcer. In a meta-

analysis of 34 studies of patients with duodenal ulcers, *H. pylor*i eradication plus antisecretory therapy was superior to an antisecretory drug alone for healing of the ulcer with a number needed to treat of 14 [147]. *H. pylori* remains an important factor also linked to the development of gastric malignancy and dyspeptic symptoms [148], thus eradication of *H. pylori* infection makes sense in view of these risks.

Antacids were the first therapeutic approach in PUD. Owing to adverse effects, lack of patient's compliance and limited cure rates, these are now rarely used for PUD. The development of the first H2RA, cimetidine, changed the management of peptic ulcers from a surgical to a medical approach. All available H2RAs induce healing rates of 70–80% for duodenal ulcers after 4 weeks, and 87–94% after 8 weeks of therapy [55]. In addition to healing duodenal ulcers, continuous daily night time dosing of H2RAs has been proven to prevent ulcer recurrence [5]. Although H2RAs are effective in the treatment of PUD, PPIs are now the preferred agents owing to their ease of use and superior efficacy. PPIs have been shown to heal peptic ulcers that may be refractory to high-dose H2RAs and they also exhibit antimicrobial activity against *H. pylori in vitro* [149].

## Duodenal ulcers

The etiology of most duodenal ulcers is due to *H. pylori*. The biologic mechanism is increased acid output, and possibly, suppression of somatostatin. Eradication in humans promotes ulcer healing [150]. PPIs alone only suppress *H. pylori* without eradication and a combination of adequate acid suppression and antibiotic therapy is necessary for the successful eradication of *H. pylori*. Omeprazole and lansoprazole inhibit gastric-acid secretion for many hours and their effect is most likely related to their ability to increase intragastric pH, which optimizes the antimicrobial action of concurrently administered drugs, such as amoxicillin. PPI-based triple therapies for PUD result in a markedly reduced ulcer recurrence rate of 12–14%, assessed from 2 weeks onwards [4].

Combinations of currently available PPIs plus clarithromycin–amoxicillin or metronidazole are standard FDA-approved treatments. Of these, omeprazole, lansoprazole and esomeprazole are approved for 10–14 day regimen. Rabeprazole can be used in a 7-day regimen based on trial data demonstrating similar results when compared with control regimens using omeprazole for 10 days [151]. European studies have demonstrated that PPI-based triple therapy can be effective in eradicating *H. pylori* in as few as 4–7 days and that such short eradication regimens enhance patient compliance and reduce the risks of drug adverse effects [101,151–155]. Treatment with PPIs twice daily is superior to treatment once daily. Successful eradication with first-line treatments varies from 70–95%, and 10-day and 14-day treatments are generally 7–9% more effective than the most commonly used 7-day regimens [4]. Taking into consideration several results of different meta-analysis, the American College of Gastroenterology recommends a 14-day course of clarithromycin triple therapy, particularly in the USA where eradication rates have typically been 80% or less with shorter durations of therapy [149].

## Gastric ulcers & NSAID-induced mucosal injury

Various strategies have been developed to prevent NSAID-induced gastropathy and some are widely implemented in clinical practice. These strategies include cotherapy with gastroprotective agents, PPIs, H2RAs, and development of the COX-2-specific inhibitors (coxibs). Interestingly, patients with gastric ulcer usually exhibit a normal or decreased basal and stimulated acid production [5,101]. NSAID-induced ulcers occur more frequently in the stomach owing to alterations in mucosal defenses. Suppression of acid remains the mainstay treatment for this disease, as maintaining a gastric pH over 3 for 18–20 h day ensures the healing of most of the gastric ulcers after 8 weeks of treatment [156,157]. Such therapeutic

outcomes are related to the duration of acid inhibitory therapy rather than to a degree of acid suppression during the day or night [158].

The relationship between NSAID use and gastroduodenal injury is well established [159]. The risk of developing endoscopically visible ulcers in patients using these drugs ranges from 15–25% [160]. Factors associated with an increased risk of developing GI complications include age over 60 years, prior history of GI ulcers, high dose of NSAIDs, use of steroid, or use of anticoagulation therapy [159].

The 2008 ACCF/ACG/AHA practice guidelines recommend selection of an NSAID based on individual risk assessment [161]. Strategies employed consist of starting at the lowest effective doses for the shortest period possible and, in high-risk patients, misoprostol or a PPI together with the NSAID or a selective COX-2 inhibitor with or without a PPI. The optimal strategy for patients who need to continue NSAID use is still debated [4], and despite the fact that mucosal protective agents, such as misoprostol, are approved for such purposes, diarrhea, even at low doses, limits its use. Healing appears to occur more rapidly with the use of PPIs than with H2RAs, misoprostol or sucralfate, although a Cochrane review suggested that high dose misoprostol (800 mg) is the only therapy that has been shown to reduce complications of perforation, hemorrhage or obstruction [70]. Actual efficacy advantages for misoprostol, if they exist, are modest, and its unpalatable side effect profile has a limited use.

Trials and meta-analysis demonstrated that among those patients requiring long-term aspirin therapy, the recurrence of a prior GI bleeding episode is less common when using concomitant PPIs and that omeprazole is superior to *H. pylori*-eradication therapy in preventing recurrent bleeding in NSAID users [46,76,81,162–164]. Despite this consistent evidence, there are substantial recurrence rates further along the treatment course of these patients. At 12-weeks duration, *H. pylori*-negative patients have been show to have relapse of their disease of up to 20% despite the use of lansoprazole [165], with relapse rates of 3 and 13% for duodenal and gastric ulcer patients, respectively, after using omeprazole for 24 weeks [166]. As most NSAIDs are dosed twice daily or are designed to provide 24 h activity, and current PPIs dosed once daily are only able to keep intragastric pH above 4 for only up to 70% of a 24 h period, patients may not be fully protected in a 24 h period against the deleterious effects of NSAIDs.

### *Helicobacter pylori* & NSAID use

There is a question of a possible synergistic interaction between *H. pylori* and NSAID use in the etiology of gastroduodenal ulcers. This was shown by a meta-analysis of endoscopic studies in NSAID takers in which uncomplicated PUD was twice as common in patients positive for compared with those negative for *H. pylori* [167]. Nevertheless, the exact contribution of *H. pylori* to ulcerogenesis and to complications in NSAID users is not clear and there is no good consensus on the optimal management of NSAID users who are infected with *H. pylori*. The role of *H. pylori* eradication in the prevention of GI pathology while on NSAIDs is not well defined, despite the role of PPIs being well established in the setting of NSAID use [168]. Nevertheless, screening for, and eradication of *H. pylori* in patients who are about to begin NSAID therapy significantly reduces the risk of ulcer development [169]. However, it is not fully elucidated whether eradication is also useful for patients who are already on long-term NSAID treatment [170,171].

Other studies have supported similar conclusions in which NSAID-naive users may benefit from testing for *H. pylori* infection and, if positive, *H. pylori* eradication therapy prior to the initiation of NSAID, whereas in chronic NSAID users *H. pylori* eradication alone seems not to protect those NSAID users with recent ulcer complications from further GI events [172].

These findings are similar to consensus reports in which *H. pylori* eradication is demonstrated to be of value in chronic NSAID users, but is insufficient to prevent NSAID-related ulcer disease completely [172,173]. Only in naive NSAID users may *H. pylori* eradication prevent peptic ulcer and bleeding, moreover, in patients receiving long-term NSAIDs and with peptic ulcer and/or ulcer bleeding, PPI maintenance treatment is better than *H. pylori* eradication in preventing ulcer recurrence and/or bleeding. Patients who are receiving long-term aspirin who bleed should be tested for *H. pylori* and, if positive, receive eradication therapy [174].

## PPI therapy for bleeding ulcers

Upper GI bleeding is a common medical condition with an annual rate of hospitalization for acute upper GI hemorrhage in the USA of 160 hospital admissions per 100,000 population, which translates into more than 400,000 per year [175]. Incidence is higher in males and increases with age [176]. Control of intragastric pH favors platelet aggregation and pepsin inhibition [177–179] and consensus statements demonstrate that rebleeding rates and the need of surgery decrease with the use of PPIs after initial control of the bleed by means of endoscopy, despite no significant changes in overall mortality [34]. This later parameter is of particular importance as the need for early endoscopy in bleeding ulcers will take precedence as a more important predictor of mortality in such patients. In a meta-analysis of endoscopic therapy for bleeding peptic ulcers, the odds ratios for mortality and rebleeding after endoscopic treatment only reached 0.55 (95% CI: 0.40–0.76) and 0.38 (95% CI: 0.32–0.45), demonstrating the importance of this technique in the management of these ulcers [76].

In patients with bleeding peptic ulcers and signs of recent bleeding, treatment with high-dose omeprazole decreases the rate of further bleeding and the need for surgery [180]. This approach suggests that using high-dose oral PPIs twice-daily may overcome the risk of rebleeding owing to the prolonged effective acid suppression of oral formulations. However, the use of intravenous formulations of PPIs at doses that include an initial bolus of 80 mg followed by continuous infusion of 8 mg/h of intravenous formulations of omeprazole or pantoprazole has become the standard when managing acute ulcer bleeding or ulcers with high-risk stigmata for bleeding [166].

## Stress-related mucosal disease

Stress-related mucosal disease refers to ulcers or mucosal erosions that occur commonly in the fundus and body of the stomach, as well as in the antrum, duodenum or distal esophagus in an ICU setting. They impose a risk of bleeding of 1.5–15% to ICU patients and an increase in mortality when the bleeding occurs [181–183]. Prophylaxis is indicated for ICU patients who are at high risk for stress ulceration. Clinical trials have demonstrated that H2RAs, PPIs and antacids reduce the frequency of overt GI bleeding in ICU patients compared with placebo or no prophylaxis [183–188].

Proton-pump inhibitors are currently used for the prevention of bleeding in the ICU setting, but their clinical efficacy has not been fully compared with H2RAs and sucralfate. Several randomized trials and meta-analyses suggest that prophylactic agents that increase gastric pH may increase the frequency of nosocomial pneumonia, compared with prophylactic agents that do not alter gastric pH, such as sucralfate [185,189–192]. While definitive evidence is lacking, it would appear that PPIs have advantage over H2RAs in the prevention of stress-induced ulcer bleeding [161].

## Expert commentary

Current medical practitioners have an amazing arsenal of safe and effective drugs for use in acid-related diseases. Therapeutic agents developed for these conditions have been success stories in drug development. The H2RAs epitomized rational, mechanism-based drug development that revolutionized the treatment of acid-related GI diseases. The PPIs represented the next step in this continuum and are the focus of most therapeutics in acid-related diseases. Their efficacy is paired with proven clinical safety, that, with expiration of patents, has led to a transition to the over-the-counter market.

It is important to highlight that despite these benefits, PPI's do not completely inhibit acid secretion. These drugs only act in those $H^+K^+$-ATPase pumps that are active [166], and as these pumps are always in a process of regeneration, more frequent doses of the PPIs may be needed for dense acid suppression. Most clinicians consider the different drugs with the PPI class as interchangeable. In broad strokes this is probably true; however, differences in the pharmacodynamic and pharmacokinetic profile of PPIs can slightly modify their clinical action and therapeutic outcome. In a similar fashion, the efficacy of intragastric pH control also may be related to *H. pylori* status and genetic polymorphisms in the CYP2C19 enzyme [101,166,193,194]. How fast and how long the intragastric target pH can be maintained above the threshold level of over 3 (PU) or over 4 (GERD) is partially a function of the systemic drug exposure of the PPI. As extensive metabolizers (EMs) of CYP2C19 have a smaller AUC than poor metabolizers (PMs), this genotype dependent difference in pharmacokinetics could translate into less acid suppression in EMs compared with PMs, with consequent poorer response to therapy in EM patients [195,196]. However, since PPIs are prodrugs that become activated in the parietal cell canaliculus, they are able to concentrate directly in the parietal cell, making systemic concentrations less of a factor in obtaining an effective response. For eradication of *H. pylori*, meta-analyses performed demonstrate variable differences in eradication rates among PMs and EMs, making polymorphisms on CYP2C19 a potential predictor of treatment response [195], improving PUD treatment and facilitating appropriate dose individualization, optimal treatment selection and drug discovery.

It should be noted that in contrast to *H. pylori* eradication, there is little overall difference in peptic ulcer healing rates among the PPIs in the management of PUD [195], and it is possible that pharmacogenomics may not explain interindividual differences enough to the extent that different dose regimens can be applied [4,197,198]. On a broader scale, a call for a pharmacogenetic-based dose alteration needs to be tempered with the global status of pharmacogenetic individualization of therapy, which remains in evolution and currently has limited application in medical practice [199]. There is a lack of consensus on how to incorporate pharmacogenetics into clinical practice, even when a limited number of alleles that are strongly and reliably associated with pharmacodynamic variability and would appear to be ideal with a narrow therapeutic index drug, such as warfarin [200,201], or in psychiatric medications, where drug response times are long and there are limited early surrogates for determination of efficacy [202]. Race and ethnicity are poor surrogates for actual determination of a patient's pharmacogenetic profile and cannot be used to tailor dosage choice with precision [203]. One meta-analysis addressing this question concluded that lansoprazole and rabeprazole have less susceptibility to *H. pylori* treatment failure owing to pharmacogenetic variants than omeprazole, and a simple drug choice rather than CYP2C19 genotyping may be more practical than genetic testing for this indication [204]. However, the subgroup comparisons for lansoprazole and rabeprazole were based on four and eight studies, respectively. Owing to the small number of subjects per study and the small number of studies, the test for heterogeneity was most likely underpowered to detect any between-study variability. Furthermore, the prevalence rate of PMs in Western Europe

and North America is low, making a potentially interesting observation less clinically relevant in these populations as those studies were largely based on the Asian population.

In the treatment of GERD, PPIs are preferred over H2RAs [66,205,206] and depending on the dose and duration of treatment, symptomatic healing rates are between 50–80% [119,207–209]. Nevertheless, a substantial number of patients with erosive esophagitis remain unhealed after 1 week of therapy with once-daily PPI therapy, especially those with high-grade disease. Moreover, there is an increasing awareness of reported nocturnal reflux and heartburn symptoms that may lead to complications such as Barrett's esophagus or sleep disorders [166]. Pharmacodynamic differences among the PPIs may translate into slight advantages in the management of patients. When given at night time, formulations such as IR-OME are reported to have an enhanced control of night time intragastric pH when compared with pantoprazole [130]; however, the daytime pH for these patients remained the same as the delayed formulations. While the IR formulation seemed to be superior, several patient still demonstrated overnight acid recovery, highlighting the need for a once-daily PPI formulation that provides better night time acid control.

Other approaches have evaluated increased doses of PPIs to achieve better intragastric pH control. A crossover study that compared the control of intragastric pH over 24 h between increasing doses of esomeprazole versus increasing doses of lansoprazole showed that higher doses of esomeprazole were better that lansoprazole but less effective than doses given twice-daily [166]. Splitting the PPIs dose into a twice a day strategy has been demonstrated to more effectively control intragastric pH [121,210]. Even on twice a day PPI, however, patients can drop their pH to less than 4 during the sleeping period [121]. These implications may be important for patient with Barrett's esophagus, as adequate overnight pH control has been proposed to decrease cell turnover and rates of dysplasia development [134,211]. The use of H2RAs in conjunction with PPI's is also a strategy that while effective in controlling intermittent night time heartburn, is not consistent for long-term acid control [166].

Suggestion of an increasing rate of esophageal adenocarcinoma and Barrett's esophagus [212], despite widespread use of current PPIs further underscore the need to improve duration of treatment, develop novel drugs based on additional physiological targets and develop treatment approaches for acid-related diseases. This has been addressed in part by the development of novel compounds such as tenatoprazole, which provides an increased half-life [213] and may prolong the time in which proton pumps are blocked. Other compounds such as the potassium competitive blockers (e.g., revaprazan, soraprazan) rapidly achieve therapeutic plasma levels and concentrate in the acidic environment of the parietal cell canaliculus. Once there, these compounds block gastric $H^+K^+$-ATPase by a $K^+$ competitive binding. They achieve their full effect quickly and provide similar acid inhibition with the first dose and subsequent, repeated doses [214]. This could potentially translate into a better nocturnal acid control and also allow rational on-demand therapy [215,216]. However, there are no commercially available potassium competitive blockers and it is not clear if an agent from this class can achieve marketing approval.

Despite areas for improvement among PPIs, they are an extremely effective class of medications. The high prevalence of acid-related disorders, expanding indications, and self-prescribed over-the-counter accessibility has resulted in millions of chronic PPI users. This trend raises the concern regarding long-term safety of these medications and potential influences in other common diseases. PPIs interfere with calcium absorption through induction of hypochlorhydria and may reduce bone resorption through inhibition of osteoclastic vacuolar proton pumps [79]. This translates into a negative calcium balance and potential bone loss, findings that are supported by several observational studies

[79,217,218]. Nevertheless, the risk for patients taking PPIs remains low and it is unclear if the attributed calcium malabsorption is severe enough to cause bone remodeling in light of a yet to be determined biologic relation between PPIs and fracture development. However, the volume of patients taking this class of medication results in the probability of clinically significant numbers of hip fractures that may be attributed to PPI therapy.

Similarly, multiple studies suggest an association between acid-suppressive therapy and development of enteric infections [82,219–221], supporting the theory that gastric acid is important in eliminating ingested bacteria and that suppression of gastric acid would result in increased susceptibility to infection. Therefore, even if this association remains unclear at present, studies like these can remind physicians that no medication is devoid of side effects and should guide duration of treatment even in the use of the most benign drug. Anecdotal observations suggest many patients are prescribed long-term PPIs without a clear indication or reassessment of need.

One important concern surrounding the safety of long-term acid-suppressive therapy relates to a possible link between PPI-induced hypergastrinemia and GI cancers, since gastrin has growth-promoting effects on a number of epithelial cell types, including cells located in the pancreatic, gastric and colonic mucosa [222,223]. It is biologically plausible that the trophic effects of gastrin may increase the chance of sporadic mutations in normal cells and/or enhance the proliferation and progression of neoplastic tissues or their precursors; however, recent studies have failed to demonstrate that long-term regular PPI therapy is associated with a significantly increased risk of colorectal cancer [224,225].

At present, the clinical choice of PPI may ultimately relate less to their specific pharmacokinetics, association with CYP polymorphisms or toxicities, and more to cost. In contrast to *H. pylori* eradication and peptic ulcer cure, treatment of GERD with PPIs does not change the natural history of disease and requires long-term therapy. It is still possible that PPI exposure for longer periods of time may be associated with relatively small, but measurable risks. These risks must be placed in the context of the indications for use, and the significant morbidity associated with inadequate acid control.

## Five-year view

The enabling knowledge of molecular physiology for gastric acid production has led physicians to have a wide array of medications that provide safe and effective control of acid production. Since the introduction of PPIs, the outcomes in the acid peptic disorders have been improved constantly; however, there are still areas of unmet needs in acid control. As with all drugs, PPIs can exhibit a large interindividual variability in drug disposition based on genetic and nongenetic factors. Differential responses are not monogenic (i.e., only CYPC19). Genotype-driven dosing of PPIs is not practical, and difficult to justify from a cost–benefit analysis at this point. However, it is clear that all therapeutics will be moving toward an individualized paradigm enabled by informatics and the use of multiple genetic and nongenetic factors. This may initially be used to identify a subset of patients at risk of therapeutic failure and could eventually be used to generate an individualized regimen for each patient in which a PPI is elected based on a less dependent CYP2C19 polymorphism in order to overcome the genetically controlled variability [213]. Moreover, patients are still refractory to PPI treatment [226] and strategies such as the need to switch PPIs, increase their dose, use multiple daily dosing or add an H2RA to the regimens may be eliminated if the initial variable response to treatment is decreased. In addition, developing new compounds or other antisecretory therapies based on documented physiologic mechanisms may be an option for the future.

As there is a significant proportion of patients on PPIs that report insufficient control of symptoms, new approaches based on increasing doses and adding additional medications, such as H2RAs, reflect the need for targeting other components of the pathophysiology of acid-related diseases. In the case of GERD, this proportion of patients may be up to 40% [227], reflecting problems with both compliance or improper dosing of PPIs, weakly acidic reflux, duodenogastric reflux, visceral hypersensitivity, psychological comorbidities, delayed gastric emptying, other conditions, such as eosinophilic esophagitis[228] and extra-GI causes of dyspepsia. Ongoing reflux of non-acid and acid material may occur during transient lower esophageal sphincter relaxations (TLESRs) and novel agents that target this motor pattern may be able to reduce symptoms. Baclofen, a GABA (B) receptor agonist, reduce the number of TLESRs, acid reflux, and symptoms but has undesirable side effects. Newer GABA (B) agonists hopefully devoid of these side effects may be of potential benefit as adjuvant therapy [229,230]. Similarly, antagonists to the metabotropic glutamate receptor 5 reported to reduce TLESRs and reflux may be of interest. In addition, novel compounds targeting centrally located cannabinoid receptors may be developed as this pathway has been demonstrated to be involved in TLESRs [231,232]. Upcoming clinical trials with these reflux inhibitors will hopefully answer the question whether reflux inhibitors may be the future of GERD therapy.

Longer-acting PPIs such as tenatoprazole (benatoprazole), a novel compound with an imidazopyridine backbone in place of the typical substituted benzimidazole, has a prolonged plasma half-life and is under development [233]. Dexrabeprazole is an *R*-isomer of rabeprazole and its efficacy has been confirmed in animal studies at half the dose of the racemate (rabeprazole) with the *R*-isomer being more effective than *S*-isomer in aspirin-induced ulcers. Pharmacokinetics in human volunteers have shown that, irrespective of the metabolizer status, the ratio of *R:S* isomers of rabeprazole in terms of $C_{max}$ was between 1.7 and 1.9, with the ratio for AUC being between 1.8 and 2.4 [234]. How this would translate into an efficacy advantage is unclear.

It is important to remember that there are a variety of causes leading to acid-related disorders. The current treatment armamentarium remains effective but is not perfect, in the face of their widespread use and chronicity of therapy, monitoring of adverse events will require strategies aimed to detect serious potential side effects only seen with long-term use of these agents. We eagerly await better therapeutic approaches to decrease the need for increasing doses and to modify the extent of the disease in these patients.

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Key issues

- Gastroesophageal reflux disease and peptic ulcer disease are common gastrointestinal disorders with the potential to progress to malignant conditions, such as adenocarcinoma.
- Physicians have a wide array of medications that provide safe and effective control of acid production but, despite their proven efficacy, there is an increasing awareness of reported nocturnal reflux and heartburn symptoms that may lead to complications such as Barrett's esophagus or sleep disorders.
- An increasing rate of esophageal adenocarcinoma and Barrett's esophagus despite use of current proton-pump inhibitors further underscores the need of improving duration of treatment, development of novel drugs based on additional physiological targets, and treatment approaches for acid-related diseases.
- Due to ample availability and chronicity of therapy, monitoring of adverse events will require strategies aimed to detect serious potential side effects only seen with long-term use of these agents; especially in the case of GERD, which will generally require long-term suppressive therapy.

**Table 1**

Pharmacological properties of histamine 2 receptor antagonists.

| Drug | Available strengths (mg) | Standard daily dose (mg) | Onset of action in h (oral) | Time to peak level (h) | Half-life (h) | Duration of action (h) | Oral bioavailability (%) | Protein binding (%) | Excretion |
|---|---|---|---|---|---|---|---|---|---|
| Cimetidine | 200<br>300<br>400<br>800 | 400 twice daily<br>800 at bedtime | 1–3 | 1–3 | 2.5–3.5 | 10–12 | 50 | 15–20 | Urinary |
| Ranitidine | 150<br>300 | 150 twice daily<br>300 at bedtime | 1 | 2–3 | 3 | 13 | 50 | 15–19 | Urinary |
| Famotidine | 20<br>40 | 20 twice daily<br>40 at bedtime | 1–3 | 1–3 | 2.5–3.5 | 10–12 | 40–60 | 15–20 | Urinary |
| Nizatidine | 150<br>300 | 150 twice daily<br>300 at bedtime | 1 | 0.5–3 | 1–2 | 10 | >70 | 35 | Urinary |

**Table 2**

Pharmacological properties of proton-pump inhibitors.

| Variable | Drug | | | | | | |
|---|---|---|---|---|---|---|---|
| | ***Rabeprazole (Aciphex®)*** | ***Pantoprazole (Protonix®)*** | ***Lansoprazole (Prevacid®)*** | ***Esomeprazole (Nexium®)*** | ***Omeprazole (Prilosec®)*** | ***Omeprazole IR – sodium bicarbonate (Zegerid®)*** | ***Dexlansoprazole (Kapidex™)*** |
| Oral dose for active and maintenance therapy of gastroduodenal ulcers (mg) | 20 | 40 | 30 | 40 | 20 | 20–40 | 30–60* |
| Available formulations | Oral | Oral iv. | Oral | Oral iv. | Oral | Oral | Oral |
| pKa | ~5 | ~4 | ~4 | ~4 | ~4 | ~4 | ~4–5 |
| Bioavailability (%) | 52 | 77 | 80–85 | 64 | 30–40 | 30–40 | NA |
| Time to peak plasma concentration (h) | 1.0–2.0 | 1.1–3.1 | 1.7 | 1.5 | 0.5–3.5 | 2 | 1–5 |
| Plasma elimination half-life (h) | 1.0–2.0 | 1.0–1.9 | 1.3–1.7 | 1–1.5 | 0.5–1.0 | 0.4–3.2 | 1–2 |
| Protein binding (%) | 96 | 98 | 97 | 97 | 95 | 95 | 96.1–98.8 |
| Urinary excretion of oral dose (%) | 30–35 | 71–80 | 14–23 | 80 | 77 | 77 | 50.7 |
| Metabolism | Hepatic | Hepatic | Hepatic | Hepatic | Hepatic | Hepatic | Hepatic |

*Dose registered for erosive esophagitis and gastroesophageal reflux disease.

iv.: Intravenous; NA: Nonavailable.