

Review

# Recent advances in proton pump inhibitors and management of acid-peptic disorders

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**Abstract**—Acid-peptic ulcers and diseases have been increasingly on rise in today's era of globalization, which is characterized by hurry, worry, and curry. This review summarizes various disorders associated with increased gastric acid secretion and various therapeutic strategies to control them. The emphasis has been laid, in particular, on the role of proton pump inhibitors (PPIs) widely used nowadays for the treatment of gastric acid diseases. The medicinal chemistry aspects and mechanism of action of irreversible PPIs and APAs have been discussed at molecular levels. The ongoing research status in this field has also been covered. Further, biological evaluation methods that can be used for screening of PPIs are also discussed in short.

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**Keywords:** Acid-peptic disorders; Therapeutic strategies; Gastric H<sup>+</sup>/K<sup>+</sup>-ATPase (proton pump); Proton pump inhibitors (PPIs); Acid pump antagonist (APAs).

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## 1. Introduction

‘Hurry, Worry & Curry’ are the causes of many disorders in today’s world of globalization. Of these acid-peptic ulcers and diseases have assumed a distinctly high proportion. The pathophysiology of acid-peptic disease is attributed to the imbalance between aggressive factors (like acid, pepsin, and *Helicobacter pylori* infection) and local mucosal defenses (like secretion of bicarbonate, mucus, and prostaglandins). Although treatment is often directed at reduction of aggressive factors, it can also be directed at strengthening mucosal defenses of stomach and duodenum.<sup>1</sup>

The inhibition of gastric acid secretion is a key therapeutic target for the ulcer diseases (viz., peptic, duodenal ulcers or that through *H. pylori* infection), gastro esophageal reflux disease (GERD), Zollinger–Ellison syndrome (Z-E), and gastritis. Currently this is achieved

by blocking the acid secretory effect of histamine (HA) through the use of H<sub>2</sub>-receptor antagonists or the irreversible H<sup>+</sup>/K<sup>+</sup>-ATPase inhibitors, popularly referred to as proton pump inhibitors (PPIs). The incidence of ulcer diseases shows global variation and their treatment should be designed to alleviate the symptoms, while keeping the risk of adverse effects to minimum. In western countries duodenal ulcers are more common, whereas in eastern countries gastric ulcers predominate. These differences are attributed to factors like diet and genetic make up. As a result the therapeutic strategies also differ from east to west. In western countries, the conventional therapy for duodenal and gastric ulcer is eradication of *H. pylori*. Whereas, in Japan unlike the west, H<sub>2</sub>-antagonists are commonly used for maintenance therapy along with the PPIs.<sup>2</sup>

The discovery of the gastric acid was the first step to understand the role of the stomach in digestion and

**Table 1.** Some landmarks in the therapy of acid-peptic disorders in past 35 years<sup>2</sup>

Year	Company/discoverer	Event/discovery
1972	James Black et al. <sup>5</sup>	Discovery of H <sub>2</sub> -receptor and H <sub>2</sub> -receptor antagonists
1973	A. Ganser & J. Forte. <sup>6</sup>	Discovery of H <sup>+</sup> /K <sup>+</sup> -ATPase (The Proton Pump)
1976	SmithKline & French. <sup>7</sup>	Cimetidine launched (H <sub>2</sub> -receptor antagonist)
1982	Allen & Hanburys Ltd <sup>8</sup>	Ranitidine launched (H <sub>2</sub> -receptor antagonist)
1988	AstraZeneca. <sup>9</sup>	Omeprazole launched (PPI)
1995	Takeda-Abbott <sup>10</sup>	Lansoprazole launched (PPI)
1997	Eisai Co. (licensed to Janssen) <sup>11</sup>	Rabeprazole launched (PPI)
2001	AstraZeneca <sup>12</sup>	Esomeprazole launched (PPI)

the diseases associated with hypersecretion of acid.<sup>3,4</sup> The drug discovery process linked with the gastric acid secretion involving H<sub>2</sub>-receptor antagonists and PPIs is summarized in Table 1. It indicates the gradual change in the focus in the treatment of gastric acid secretion disorders.<sup>2</sup>

In this review, various disorders related with increased gastric acid secretion and therapeutic strategies to control them have been summarized. Furthermore, emphasis has been laid on the role of PPIs in particular for the treatment of gastric acid disorders. The medicinal chemistry aspects of this particular class of compounds are also discussed.

### 1.1. Mechanism of gastric acid secretion

Stomach is a primary site of digestion. Presence of food stimulates release of acids and enzymes in stomach. The chemo- and mechanosensitive receptors present in stomach are triggered by presence of food to produce specific responses.<sup>2</sup> The acid secreting parietal cell is the principle cell in gastric glands. The physiological regulation of acid secretion by the parietal cells is thus an important factor behind the rationale of use of various agents to reduce gastric acidity. Three major pathways activating parietal acid secretion include: (1) neuronal stimulation via the vagus nerve, (2) paracrine stimulation by local release of histamine from enterochromaffin-like (ECL) cells, and (3) endocrine stimulation via gastrin released from antral G cells. In neuronal pathway, acetylcholine (ACh) released by vagal nerve directly stimulates gastric acid secretion through muscarinic M<sub>3</sub> receptors located on the basolateral membrane of parietal cells. The CNS is considered to be the chief contributor for initiating gastric acid secretion in response to the anticipation of food. ACh indirectly stimulates release of histamine from enterochromaffin-like (ECL) cells in the fundus and gastrin from the G cells in the gastric antrum. ECL cells, the sole source of gastric histamine involved in acid secretion, are present in close proximity to parietal cells. Histamine released from ECL cells activates parietal cells in paracrine fashion by binding to H<sub>2</sub> receptors. Gastrin is primarily present in antral G cells. Release of gastrin is under regulation of central neural activation, local distension, and chemical composition of gastric content. Gastrin stimulates parietal cells by binding with gastrin receptors. Gastrin also exerts its action in an indirect manner by causing the release of histamine from ECL cells.<sup>1</sup> Binding to respective G-protein coupled receptors by ACh, gastrin, and histamine results in activation of second-messenger systems.<sup>2</sup> Vagal stimulation and the action of gastrin (from duodenal and antral G cells) stimulate release of histamine from paracrine-ECL cells or mast cells. Increased levels of both intracellular Ca<sup>2+</sup> by gastrin/ACh and cyclic AMP by histamine finally cause acid secretion.<sup>13</sup> The final step in acid secretion is mediated by H<sup>+</sup>/K<sup>+</sup>-ATPase, also called as gastric proton pump.<sup>14</sup> Activation of either the cAMP or Ca<sup>2+</sup>-dependent pathway or both causes stimulation of H<sup>+</sup>/K<sup>+</sup>-ATPase on parietal cells<sup>15</sup> (Fig. 1).

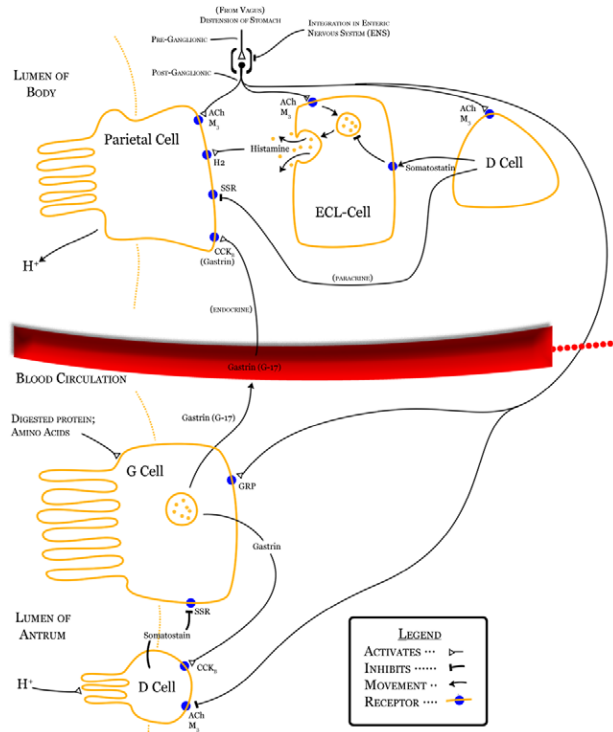
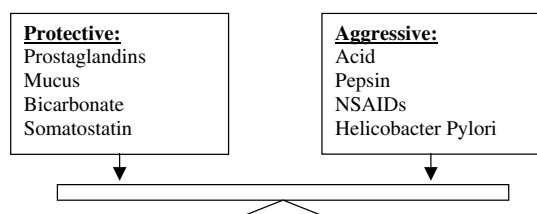


Figure 1. Mechanism of gastric acid secretion.<sup>16</sup>

### 1.2. Disorders associated with elevated secretion of gastric acid

- (a) *Peptic ulcers*: Neuropeptide Y, corticotrophin-releasing factor, bombesin, calcitonin, neurotensin, interleukin 1, along with somatostatin, prostaglandins, bicarbonates, and mucin act as mucosal defense factors. Imbalance between these mucosal defense factors and aggressive factors (acid and pepsin) is involved in peptic ulcers<sup>2</sup> (Fig. 2). Their rational treatment is aimed at restoring this balance. In case of duodenal ulcers (DU), there is increase in basal acid secretion. In gastric ulcers (GU), however, there is weakening of mucosal defenses that can lead to injury in spite of low acid secretion. Differences between DU and GU are summarized in Table 2. *H. pylori* and non-steroidal anti-inflammatory drugs (NSAIDs) play important role in ulcer induction.<sup>1</sup> Particularly NSAIDs inhibit production of prostaglandins from arachidonic acid by inhibiting enzyme cyclooxygenase (COX). Chronic NSAID users are at 2–4% risk of developing a symptomatic ulcer, gastrointestinal bleeding or associated perforation. In ulcer patients, NSAIDs increase the risk of probable complications fourfold. Further, these complications may remain undetected because of reduction in pain, thereby worsening the condition. Co-administration of Misoprostol, the synthetic prostaglandin analog or acid suppression therapy may be beneficial. Proton pump inhibitors are superior to H<sub>2</sub>-receptor antagonist in promoting healing and preventing recurrence of both GU and DU (see Fig. 2).



**Figure 2.** Factors involved in maintaining acid balance.

- (b) *Zollinger–Ellison (Z-E) syndrome*: In this disease, a non- $\beta$  cell tumor of the pancreatic islets may produce gastrin in a quantity sufficient to stimulate the secretion of gastric acid to life-threatening levels. This can lead to severe gastroduodenal ulcerations and other consequences of the uncontrolled hyperchlorhydria. The therapy is aimed at reducing gastric acid secretion. In this the proton pump inhibitors being surely the drugs of choice.<sup>2</sup> ECL-cells carcinoids are rare events that have been described in association with Z-E syndrome.<sup>19</sup>
- (c) *Helicobacter pylori (H. pylori) infection*: Around 40% of patients over 40 years age and with peptic ulcer disease are infected with *H. pylori* infection. *H. pylori* is a gram-negative rod-shaped bacteria and has clearly been associated with gastritis, peptic ulcers, gastric adenocarcinoma, and gastric  $\beta$ -cell lymphoma. Up to 80–90% of ulcers may be associated with *H. pylori* infection of stomach. This infection may lead to impaired production of somatostatin by D cells. This results into increased gastric acid secretion along with impaired duodenal bicarbonate production.<sup>1</sup> *H. pylori* infection is now

proven to be a risk factor for gastric cancer and the organism was classified as group-I carcinogen by WHO.<sup>20</sup> *H. pylori* infection also causes inflammation of the antral gastric mucosa. Bacterial products and inflammatory cytokines may produce changes in the endocrine function.<sup>21</sup> It has now become a standard care procedure to eradicate the infection in patients with gastric and duodenal ulcers. This strategy is almost successful in eliminating the risk of ulcer recurrence (Fig. 4).<sup>1</sup>

- (d) *Gastro esophageal reflux disease (GERD)*: It is a disorder of defense mechanism at the esophageal junction, caused by regurgitation of the gastric contents, especially of gastric acid. GERD is associated with decreased gastric emptying and/or increased incidence of transient lower esophageal relaxation (T-LESR).<sup>23</sup> Smoking and obesity increase the incidence of GERD symptoms like heartburn, belching, and bloating. GERD is not life-threatening, but can cause significant discomfort and increased risk of Barrett's esophagus.<sup>2</sup> Relationship between GERD symptoms and incidence of esophageal adenocarcinoma has also been suggested. It has also been linked to tracheopulmonary symptoms like laryngitis and asthma. Besides disturbed gastrointestinal motility, injurious effects of the acid-peptic refluxate on the esophageal epithelium are also responsible for GERD symptoms. Hence along with prokinetic drugs, suppression of gastric acid is the current pharmacotherapeutic approach for its treatment.<sup>1</sup> *H. pylori* infection does not necessarily correlate with GERD, although a reduction in acid secretion reduces chances of reflux.<sup>23</sup>

**Table 2.** Distinguishing features of the two major forms of peptic ulcers<sup>18</sup>

Serial No.	Features	Duodenal ulcer	Gastric ulcer
1	Incidence	Four times common than gastric ulcers Usual age 25–50 years More common in males than in females (4:1)	Less common than duodenal ulcers Usually beyond 6th decade More common in males than in females (3.5:1)
2	Etiology	Most commonly as a result of <i>Helicobacter pylori</i> infection Other factors are hypersecretion of acid-pepsin, association with alcoholic cirrhosis, tobacco, hyperparathyroidism, chronic pancreatitis, blood group O, genetic factors, etc.	Gastric colonization with <i>H. pylori</i> asymptomatic but higher chances of development of duodenal ulcers. Disruption of mucus barrier most important factor. Association with gastritis, bile reflux, drugs, alcohol, and tobacco
3	Pathogenesis	Mucosal digestion from hyperacidity most significant factor Protective gastric mucus barrier may be damaged	Usually normal-to-low acid levels; hyperacidity if present is due to high serum gastrin Damage to mucus barrier is a significant factor
4	Pathological changes	Most common in the first part of duodenum Often solitary, 1–2.5 cm in size, round to oval, punched out	Most common along the lesser curvature and pyloric antrum Grossly similar to duodenal ulcers
5	Complications	Commonly hemorrhage, perforation, sometimes obstruction, are observed. However, malignant transformation never occurs	Perforation, hemorrhage and at times obstruction, are common. Malignant transformation less than 1% cases
6	Clinical features	Pain food relief pattern Night pain common No vomiting Melaena more common than hematemesis No loss of weight No particular choice of diet Marked seasonal variation Occurs more commonly in people at greater stress	Food pain pattern No night pain Vomiting common Hematemesis more common Significant loss of weight Patients choose bland diet devoid of fried food, curries etc. No seasonal variation More often in laboring groups

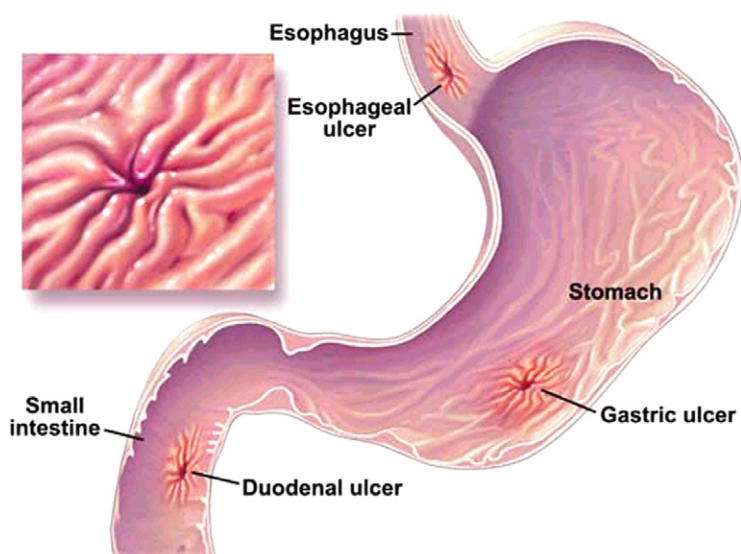


Figure 3. Peptic ulcer.<sup>17</sup>

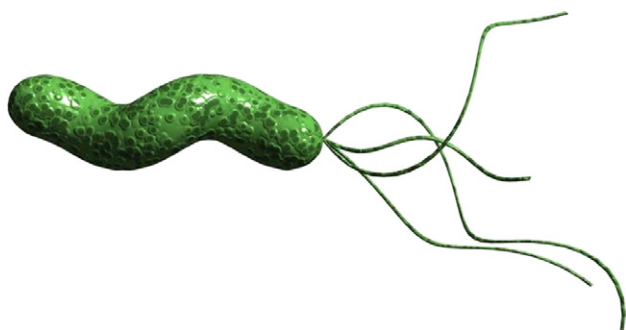


Figure 4. *Helicobacter pylori*.<sup>22</sup>

- (e) *Stress-related ulcers*: These are the ulcers of stomach and duodenum that usually occur as a result of severe systemic or CNS illness or trauma. Both acid and mucosal ischemia are involved in the etiology of stress ulcers. Similarly, stress due to physiological factors like septicemia, intracranial lesions, alcohol intake, and smoking can also appreciably contribute to ulcer induction. Intravenous  $H_2$ -receptor antagonist and intravenous PPIs are preferred agents for its treatment.<sup>1</sup>
- (f) *Non-ulcer dyspepsia*: It refers to ulcer-like symptoms in patients who are without overt gastroduodenal ulceration. Though pathogenesis of this syndrome remains unclear, it may occur because of gastritis or use of NSAIDs. Empirical treatment with acid-suppressive agents is used routinely.<sup>1</sup>

### 1.3. Complications arising from the disorders associated with elevated secretion of gastric acid<sup>18</sup>

**1.3.1. Obstruction.** Development of fibrous scar at or near the pylorus results in pyloric stenosis.

**1.3.2. Hemorrhage.** Minor bleeding by erosion of small blood vessels in the base of an ulcer occurs in all the

ulcers and can be detected by testing the stool for occult blood.

**1.3.3. Malignant transformation.** The dictum ‘*cancers ulcerate but ulcers rarely cancerate*’ holds true for most peptic ulcers. A chronic duodenal ulcer never turns malignant, while less than 1% of chronic gastric ulcers may transform into carcinoma.

**1.3.4. Perforation.** Perforation occurs more commonly in chronic duodenal ulcers than chronic gastric ulcers. Following sequel may result.

- (i) On perforation the contents escape into the lesser sac or into the peritoneal cavity, causing acute peritonitis.
- (ii) Air escapes from the stomach and lies between the liver and the diaphragm giving the characteristic radiological appearance of air under the diaphragm.
- (iii) Perforation may extend further to involve adjacent organs (liver and pancreas).

## 2. Therapeutic strategies

Acid secretion is a physiologically important process of the stomach as:

1. Acid induces pepsinogen activation to initiate digestive process and
2. It kills bacteria and other microbes ensuring a stable intragastric environment. However, under certain circumstances secretion of large excess of gastric acid and pepsinogen injures the gastroduodenal mucosa and causes serious and fatal ulcerations.<sup>15</sup> Hence, there is a need of good gastric acid secretion inhibitors.

The secretion of gastric acid occurs at the level of parietal cells of oxyntic glands in the gastric mucosa, producing 2–3 L of gastric juice per day (HCl of pH 1).<sup>24</sup>

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