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A Review on Proton Pump Inhibitors and Its Release in Gastro Intestinal Tract

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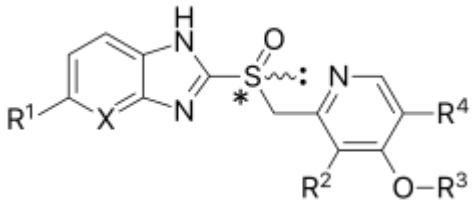
ABSTRACT

Proton pump inhibitors represent a class of medications used to treat a wide variety of pathologies related to the stomach's acid production. This activity reviews the indications, action, contraindications for proton pump inhibitors as a valuable agent in managing acid-related disorders. PPIs are used to treat gastrointestinal conditions such as gastro-oesophageal reflux disease (GERD) and peptic ulcer disease (PUD) or in patients who may be at high risk for these diseases (e.g. patients on non-steroidal anti-inflammatories [NSAIDs] and anti-platelet therapy). Although clinically important adverse effects of PPIs can occur, just as with other drugs, those are not frequently observed during or after administration. This activity will highlight the mechanism of action, adverse event profile, and other key factors (e.g., off-label uses, dosing, pharmacodynamics, pharmacokinetics, monitoring, relevant interactions) pertinent for members of the interprofessional team in the treatment of acid-related disorders.

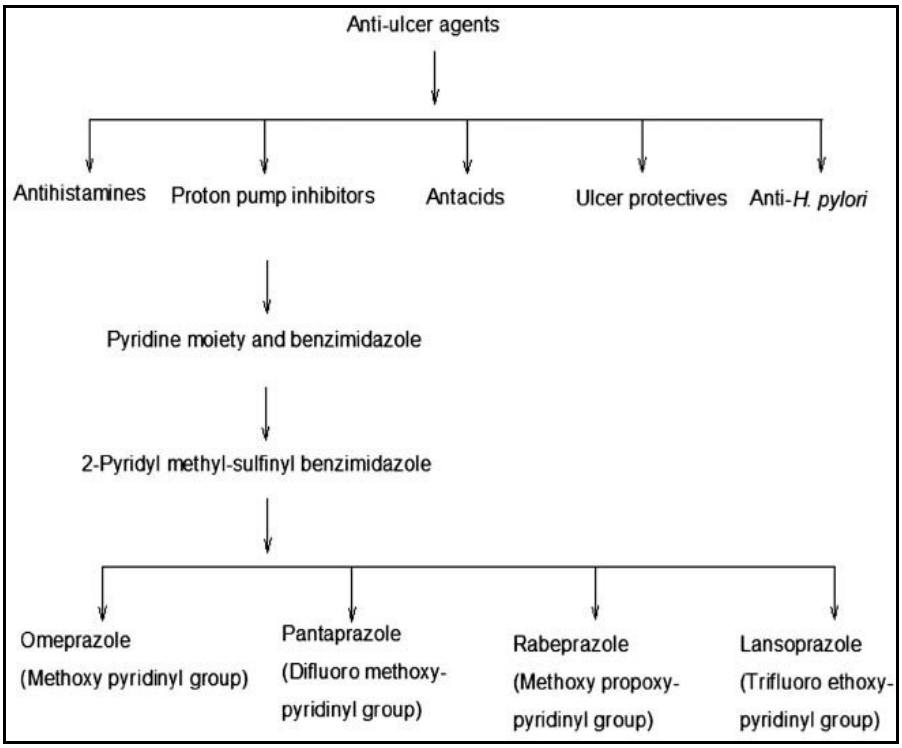
INTRODUCTION

Proton-pump inhibitors (PPIs) are a class of medications that cause a profound and prolonged reduction of stomach acid production. They do so by irreversibly inhibiting the stomach's H+/K+ ATPase proton pump.

They are the most potent inhibitors of acid secretion available. Proton-pump inhibitors have largely superseded the H2-receptor antagonists, a group of medications with similar effects but a different mode of action, and heavy use of antacids. PPIs are among the most widely sold medications in the world. The class of proton-pump inhibitor medications is on the World Health Organization's List of Essential Medicines. Omeprazole is the specific listed example.

Proton-pump inhibitor	
Drug class	
 **General structure of a proton-pump inhibitor**	
Class identifiers	
Use	Reduction of gastric acid production
ATC code	A02BC
Mechanism of action	Enzyme inhibitor
Biological target	H^+/K^+ ATPase

CLASSIFICATION OF PROTON PUMP INHIBITORS



EXAMPLES:

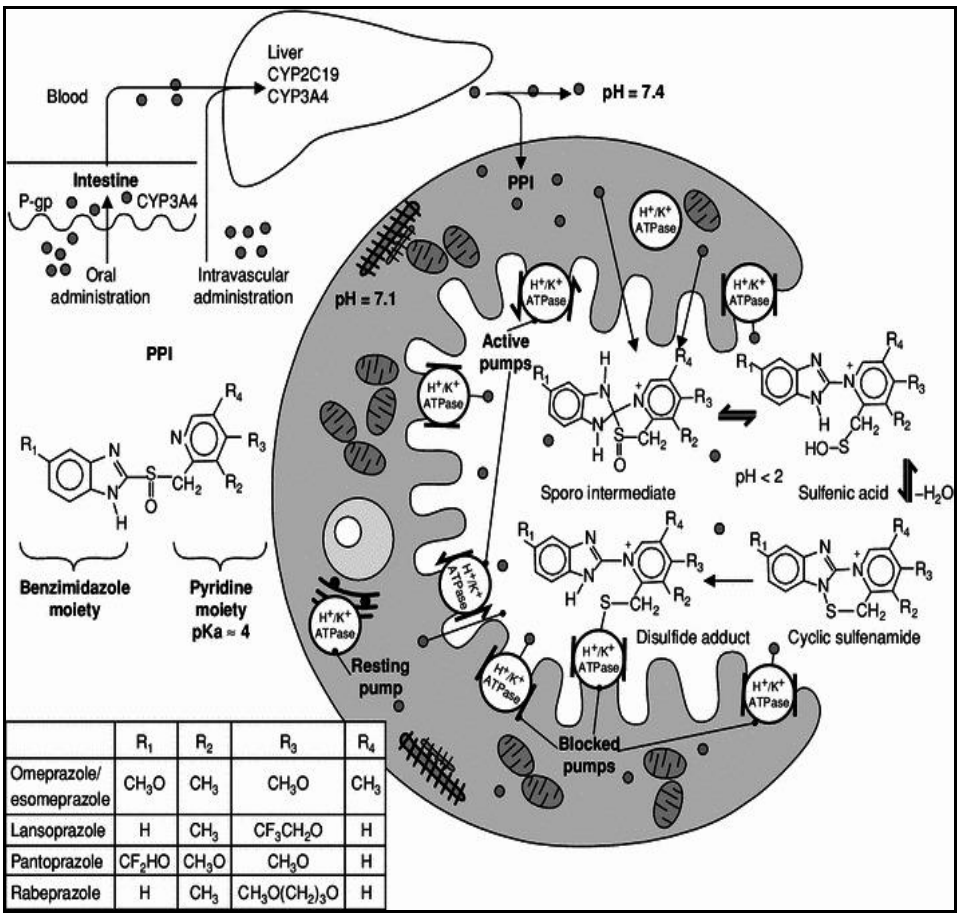
Medically used proton pump inhibitors:

- Omeprazole
- Esomeprazole
- Lansoprazole
- Dexlansoprazole
- Pantoprazole
- Rabeprazole

PHYSIOLOGY OF GASTRIC ACID SECRETION

The pharmacodynamics and pharmacokinetics of PPIs are integrally linked to the physiology and structure of the enzyme responsible for gastric acid secretion by the parietal cell, the H+–K+-adenosine triphosphatase (H+–K+-ATPase). This extraordinary acid pump creates a 1-million-fold gradient in H+ concentration from inside the parietal cell to the gastric lumen in

return for inward transport of K+. Without stimulation, the H+–K+-ATPase enzyme resides in the parietal cell cytoplasm in a relatively inactive tubulovesicle form. This ATPase can be stimulated to secrete gastric acid by the binding of different ligands, such as acetylcholine, histamine, or gastrin. Histamine can be released by the enterochromaffin-like cells directly or after stimulation of these cells by gastrin, which is released after a meal. Histamine then binds to the histamine H2 receptor and stimulates the H+–K+-ATPase to release intracellular second messengers, cyclic adenosine monophosphate (cAMP), and Ca2+, leading to acid release.



	R_1	R_2	R_3	R_4
Omeprazole/ esomeprazole	CH_3O	CH_3	CH_3O	CH_3
Lansoprazole	H	CH_3	CF_3CH_2O	H
Pantoprazole	CF_2HO	CH_3O	CH_3O	H
Rabeprazole	H	CH_3	$CH_3O(CH_2)_3O$	H

Figure 1: General chemical structure and mechanism of action of proton pump inhibitors (PPIs). ATPase adenosine triphosphatase, CYP cytochrome P450, P-gp P-glycoprotein, pKa negative logarithm of the acid ionization constant.

MECHANISM OF ACTION

Proton pump inhibitors act by irreversibly blocking the hydrogen/potassium adenosine triphosphatase enzyme system (the H+/K+ ATPase, or, more commonly, the gastric proton pump) of the gastric parietal cells. The proton pump is the terminal stage in gastric acid secretion, being directly responsible for secreting H+ ions into the gastric lumen, making it an ideal target for inhibiting acid secretion. Because the H,K-ATPase is the final step of acid secretion, an inhibitor of this enzyme is more effective than receptor antagonists in suppressing gastric acid secretion. All of these drugs inhibit the gastric H,K-ATPase by covalent binding, so the duration of their effect is longer than expected from their levels in the blood.

Targeting the terminal step in acid production, as well as the irreversible nature of the inhibition, results in a class of medications that are significantly more effective than H2 antagonists and reduce gastric acid secretion by up to 99%.

Decreasing the acid in the stomach can aid the healing of duodenal ulcers and reduce the pain from indigestion and heartburn. However, stomach acids are needed to digest proteins, vitamin B12, calcium, and other nutrients, and too little stomach acid causes the condition hypochlorhydria.

The PPIs are given in an inactive form, which is neutrally charged (lipophilic) and readily crosses cell membranes into intracellular compartments (like the parietal cell canaliculus) with acidic environments. In an acid environment, the inactive drug is protonated and rearranges into its active form. As described above, the active form will covalently and irreversibly bind to the gastric proton pump, deactivating it.

In H. pylori eradication, PPIs help by increasing the stomach pH, causing the bacterium to shift out of its coccoid form which is resistant to both acids and antibiotics. PPIs also show some weaker additional effects in eradication.

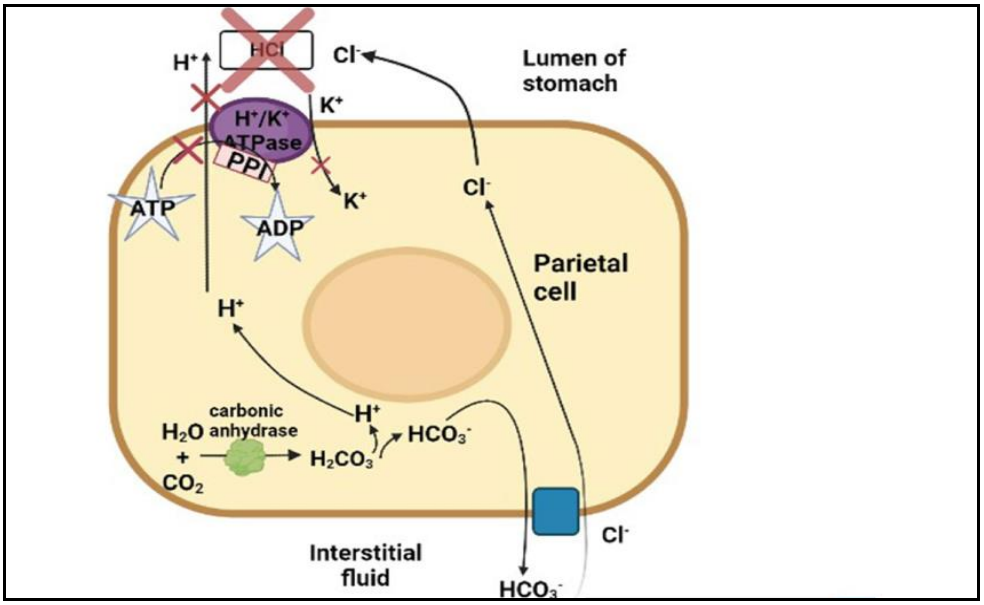


Figure 2: The Activation Of PP

ACTIVATION OF THE PROTON PUMP INHIBITORS (PPIS) FOR BINDING TO THE H+–K+-ATPASE

PPIs must be activated to bind to the CYSs of the ATPase, and the rate of this activation varies with their structures. These PPIs are weak bases that are acid labile and must be formulated with an enteric coating to resist gastric acid degradation and allow absorption in the more alkaline environment of the small intestine. Currently approved PPIs have a very similar basic structure that combines a benzimidazole ring and a pyridine ring through a sulfinyl linkage. The first PPI discovered was timoprazole, which lacked any substitutions on these rings in contrast to currently approved PPIs with various substitutions that affect their chemistry. For the sulfinyl to chemically bind to the CYSs of the ATPase, it has to gain energy from the acidic environment inside the parietal cell.

Activation of the PPI occurs by addition of two protons to the nitrogen's on either side of the sulfinyl group. Once it is activated, the PPI can inactivate the proton pump by binding to CYS molecules on the ATPase to form disulfide bonds. The PPIs have two pKa (negative logarithm of the acid ionization constant) values that influence their activation. The first pKa ranges from 3.83 to 4.53 and leads to ionization and accumulation in the acidic region of the parietal cell canaliculus where acid is being secreted, with pH around 1.0. This is the most acidic cytoplasm of any cell within the body. The second pKa of approved drugs ranges from 0.11 to 0.79. This second protonation on the benzimidazole causes rearrangement of the

sulfinyl into a cationic sulfenic acid or a sulfenamide, which has the energy to react with the cysteine sulfhydryl's to form one or more covalent disulfide bonds.

Table 1: Chemical properties and the presence (indicated by +) of specific cysteine (CYS) binding sites of proton pump inhibitors

Proton pump inhibitor	pKa1	pKa2	CYS321	CYS813	CYS822	CYS892
Omeprazole	4.06	0.79		+		+
Lansoprazole	3.83	0.62	+	+		
Pantoprazole	3.83	0.11		+	+	
Rabeprazole	4.53	0.62		+		
Tenatoprazole	4.04	-0.12		+	+	

The PPI can bind to several different CYSs on the proton pump. The speed with which these two activation reactions occur influences which CYS(s) it will bind. All the PPIs bind to CYS813 located on the acidic luminal side within the proton transporter, which stops proton transfer. This location is easily accessible to the PPIs for binding, but it is also accessible to reducing agents, such as glutathione and dithiothreitol, which can release the PPI and reactivate the transporter. In contrast, the CYS at position 822 located deep within the sixth transmembrane segment of the ATPase reacts with the PPIs that are activated more slowly, such as pantoprazole and tenatoprazole. CYS822 is relatively inaccessible to reducing agents so the disulfide bonds created by the PPI permanently inactivate the proton pump. This difference in binding sites accounts for some of the dynamic differences among PPIs according to those with reversible binding and those that are inaccessible to reduction of the disulfide bonds. Before inactivation of the proton pump can occur, the PPI must reach the acidic site of action within the parietal cell while the proton pump is active for it to undergo the acidic activation described above. The concentration at the site of action is determined by the PPI's pharmacokinetics, beginning with absorption in an inactive form, distribution, metabolism by cytochrome P450 (CYP) 2C19 or CYP3A4, and elimination. The rate of metabolism is under developmental as well as genetic control, which confounds accurate prediction of these rates.

Table 2. Pharmacokinetic properties of proton pump inhibitors

Agent	Bioavailability	Cmax	AUC 0-24	Excretion	pKa
Omeprazole	45%	0.7	2.0	Renal	4.0
Lansoprazole	85%	0.5-1.0	2.5	Biliary	4.0
Rabeprazole	52%	0.4	0.8	Renal	5.0
Pantoprazole	77%	2.5	5.0	Renal	3.9
Esomeprazole	64%	1.5	4.3	Renal	4.0

ADVANTAGES:

- PPIs are highly effective at reducing stomach acid, which helps alleviate symptoms of acid-related conditions.
- They promote the healing of inflammation and damage in the oesophagus caused by stomach acid.
- PPIs provide significant relief from symptoms such as heartburn, acid reflux, and indigestion.
- They help prevent the formation of gastric and duodenal ulcers, especially in patients taking NSAIDs (nonsteroidal anti-inflammatory drugs).
- The effects of PPIs last longer compared to other acid-reducing medications like H2 blockers, providing sustained symptom relief.
- By effectively managing symptoms and healing ulcers, PPIs can reduce the need for surgical interventions in severe cases.
- Effective symptom management can significantly improve the quality of life for patients with chronic acid-related conditions.

DISADVANTAGES:

- Chronic use of PPIs can lead to several health issues, including vitamin B12 deficiency, magnesium deficiency, and calcium malabsorption, which can increase the risk of fractures.
- PPIs can increase the risk of gastrointestinal infections like Clostridium difficile, as well as respiratory infections such as pneumonia, due to the reduction of stomach acid that normally helps kill harmful bacteria.

- Long-term use has been associated with an increased risk of chronic kidney disease and acute interstitial nephritis.

- Discontinuing PPIs suddenly can lead to a rebound increase in stomach acid production, causing symptoms to return and sometimes worsen.

- PPIs can interact with other medications, such as certain anticoagulants, antifungals, and antiretrovirals, potentially altering their effectiveness.

- Some studies have suggested a potential link between long-term PPI use and an increased risk of cardiovascular events, although this is still under investigation.

- There have been concerns about a possible association between long-term PPI use and an increased risk of dementia, though evidence is not conclusive.

- PPIs can mask the symptoms of more serious underlying conditions, such as gastric cancer, delaying diagnosis and treatment.

LIMITATIONS:

- PPIs are less effective for non-erosive reflux disease (NERD) compared to erosive esophagitis.

- PPIs typically take longer to provide relief compared to antacids or H2 blockers. They need to be taken consistently over several days to achieve full effectiveness.

- PPIs are often overprescribed or used without proper medical indication, leading to unnecessary exposure to their risks.

- Due to potential long-term side effects, PPIs are generally recommended for short-term use unless there is a strong medical need for prolonged therapy.

- Some patients may not experience complete relief of symptoms, requiring additional or alternative treatments.

- Prolonged use can lead to dependence, and stopping PPIs suddenly can cause rebound acid hypersecretion, making symptoms worse.

- Although generic versions are available, the cost of PPIs can be higher compared to other acid-reducing medications, especially for prolonged use.

ADVERSE EFFECTS

As the usage of PPIs continues to rise, it becomes extremely important to understand the extent of their adverse effects. As the use of these medications is common, potential adverse effects have received significant media attention; however, it is essential to note that most of these associations have as their basis on low-grade evidence and observational associations rather than clear causation. The following is a description of the variety of adverse effects described in the literature.

Hypomagnesemia

Albeit a rare side-effect, PPIs may lower magnesium to a level not easily replenished by supplementation and only corrected with removal of PPI. Hypomagnesemia is a serious complication that predisposes the patient to tetany, seizure, muscle weakness, delirium, and cardiac arrhythmias. It is not yet entirely clear what causes this adverse effect, but one hypothesis suggests that it may be due to decreased active intestinal absorption of magnesium by the transient receptor protein channels (TRPM 6/7) that are stimulated by extracellular protons.

Infection

While the acidic environment of the stomach serves as an environment in which proteins become activated to perform certain functions, so too does it serve as a chemical barrier against bacterial infection. PPIs have correlations with an increased amount of Clostridium difficile infections, other enteric foodborne infections, and potentially increased risk of community-acquired pneumonia. While it is still unclear as to the exact mechanism for this increased infection risk, one hypothesis proposed that the decreased acidic environment of the stomach leads to bacterial overgrowth and increased risk of bacterial aspiration.

Rebound Acid Secretion

PPIs can increase the levels of gastrin, which in turn leads to increased proliferation of ECL cells. ECL cells produce histamine, which under normal circumstances, stimulates parietal cells to activate their H+/K+ ATPase and produce acid into the stomach. Because PPIs act a step further than histamine, this side-effect does not negate the effect of PPIs. However, the problem lies in the discontinuation of PPIs after prolonged use, which has been shown in

some cases to result in acid levels higher than before the initiation of PPIs. This effect has been referred to as rebound acid secretion.

Vitamin Deficiency

When vitamin B12 enters the stomach, it is bound to a protein molecule, R-factor. For vitamin B12 to release from R-factor, proteases need to be activated by an acidic environment. Once activated, the peptidases release R-factor from vitamin B12 so that it may bind another molecule, intrinsic factor, for absorption at the level of the terminal ileum. Disruption of the stomach's acidic environment by PPIs may lead to a vitamin B12 deficiency, although this appears to be clinically rare. Additionally, iron deficiency has also been reported with prolonged PPI use, although the exact mechanism remains elusive. There is also slight malabsorption of insoluble calcium separate from food, which many believe to be subclinical in most cases.

APPLICATIONS:

These medications are used in the treatment of many conditions, such as:

- Dyspepsia
- Peptic ulcer disease including after endoscopic treatment for bleeding
- As part of Helicobacter pylori eradication therapy
- Gastroesophageal reflux disease (GERD or GORD) including symptomatic endoscopy-negative reflux disease and associated laryngopharyngeal reflux causing laryngitis and chronic cough
- Barrett's oesophagus
- Eosinophilic esophagitis
- Stress gastritis and ulcer prevention in critical care
- Gastrinomas
- Zollinger–Ellison syndrome (often 2–3x the regular dose is required)

CONTRAINDICATIONS:

PPI contraindications include patients with known hypersensitivity to that class of drugs, and their use requires caution in patients with severe hepatic disease. As mentioned above, PPIs undergo metabolism by the cytochrome P450 system of the liver, mostly by CYP2C19; hence, any severe dysfunction in this metabolization serves as a relative contraindication. That said, clinically, clinicians often use PPIs in patients with severe liver disease with increased monitoring. PPIs can also alter the activity of specific cytochrome enzymes and delay the clearance of certain drugs such as phenytoin, warfarin, and diazepam. As such, the use of these drugs requires caution in those undergoing PPI therapy. Furthermore, the stomach's acidic environment is necessary for the effective absorption of ketoconazole, and it is advisable to use other antifungals in the setting of long-term PPI use. Conversely, the same acidic environment potentiates the absorption of digoxin, and thus this drug's use merits extreme caution due to the severity of its side-effect profile.

ADMINISTRATION:

The formulations of PPIs are often specifically designed to prevent premature activation by gastric acid. The delivery methods include:

- Enteric-coated tablets
- Gelatine capsules
- Coated granules as a suspension
- In combination with bicarbonate to temporarily neutralize luminal gastric acid
- For immediate acid suppression, there are intravenous formulations for lansoprazole, pantoprazole, and esomeprazole.

As proton pumps recycle periodically in the stomach, it may take a few days for PPIs to achieve a full effect - and of note, their duration of action is slower than some other medications that affect acid production, such as histamine-receptor blockers. These medications are best administered before food intake as proton pumps become activated during meals, and administration of PPIs prior to food intake will enhance the drug's efficacy. For this reason, most practitioners recommend that the patient take the PPI first thing in the morning when taken once daily. If twice-daily dosing is employed, then a second dose is

usually added approximately 30 minutes before dinner. For some select patients with nighttime predominance of symptoms, the timing of once-daily administration may change to 30 minutes pre-dinner.

CONCLUSION:

Without activation through ligand binding by histamine, gastrin, acetyl choline, or other mediators, the parietal cell acid pump (H+–K+-ATPase) is inactive and cannot be inhibited. H+–K+-ATPase must be activated to secrete gastric acid, which is needed for the PPI to be activated in order to bind to the enzyme to cause inhibition. The pharmacokinetics of the PPIs, especially the absorption rate and tmax, must be considered in the dosing schedule for a PPI so it is present in the circulation when the proton pump is active. This usually requires administration of the PPI 60–90 min before a meal. The site of binding of the different activated PPIs to different CYSs in the H+–K+-ATPase influence the reversibility of the proton pump inactivation and the duration of inhibition.

FUTURE SCOPE:

- Research is ongoing to develop PPIs with enhanced efficacy, faster onset of action, and prolonged duration of effect. New delivery systems, such as immediate-release formulations and combination therapies, aim to improve patient compliance and therapeutic outcomes.

- Advances in pharmacogenomics may allow for more personalized PPI therapy, tailoring treatment based on individual genetic profiles to optimize efficacy and minimize adverse effects.

- As concerns about the long-term use of PPIs grow, research into alternative therapies for acid-related disorders is expanding. This includes the development of potassium-competitive acid blockers (P-CABs), which may offer similar benefits with potentially fewer side effects.

- Continued research into the long-term safety of PPIs is crucial. Large-scale, long-term studies are needed to better understand the risks associated with chronic use and to develop strategies to mitigate these risks.

- Further investigation into the mechanisms underlying PPI-associated adverse effects, such as nutrient deficiencies, bone fractures, and renal issues, can lead to improved management strategies and the development of safer alternatives.

- Updating clinical guidelines to reflect the latest research and educating healthcare providers and patients about the appropriate use of PPIs will be important in optimizing their use and minimizing potential harm.

- Exploring the use of PPIs in combination with other drugs for conditions like H. pylori infection, Zollinger-Ellison syndrome, and nonsteroidal anti-inflammatory drug (NSAID)-induced ulcers can improve treatment outcomes.

- Emphasizing lifestyle modifications, dietary changes, and other non-pharmacological approaches to managing acid-related disorders can reduce the reliance on PPIs and improve overall patient health.

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