



Comparative Analysis of PPIs vs. H2RAs in Gastrointestinal Therapy: Efficacy, Safety, and Cost

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ABSTRACT

This review article provides an in-depth comparative analysis of Proton Pump Inhibitors (PPIs) and Histamine-2 Receptor Antagonists (H2RAs) in the treatment of gastrointestinal disorders, focusing on efficacy, safety, and economic considerations. PPIs and H2RAs are widely used to manage conditions such as gastroesophageal reflux disease (GERD), peptic ulcer disease, and Zollinger-Ellison syndrome. This article evaluates numerous clinical studies and meta-analyses to discern the therapeutic advantages and limitations of both drug classes.

Efficacy is examined through clinical trial outcomes, highlighting PPIs' superior acid suppression and longer duration of action compared to H2RAs. PPIs are shown to provide more effective and sustained symptom relief, particularly in severe GERD and erosive esophagitis. Safety profiles are scrutinized, noting that while both drug classes are generally well-tolerated, PPIs are associated with increased risks of long-term adverse effects such as bone fractures, renal disease, and vitamin B12 deficiency. Conversely, H2RAs have a lower incidence of severe adverse effects but are less potent, potentially leading to incomplete symptom control in some patients.

Economic aspects are also discussed, considering drug costs, long-term healthcare expenses, and the impact on quality of life. PPIs, despite being more expensive upfront, may reduce overall healthcare costs by decreasing the need for further medical interventions due to their higher efficacy. The review concludes with recommendations for clinical practice, advocating for a balanced approach that considers individual patient needs, potential risks, and cost-effectiveness, ensuring optimal therapeutic outcomes in gastrointestinal disorder management.

Keywords: Proton pump inhibitors (PPIs), histamine-2 receptor antagonists (H2RAs), gastroesophageal reflux disease (GERD), Cost-effectiveness

INTRODUCTION

Proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs) are vital in treating various gastrointestinal disorders worldwide, including dyspepsia, peptic ulcer disease (PUD), gastroesophageal reflux disease (GERD), and *Helicobacter pylori* (*H. pylori*) infection. They are commonly prescribed to alleviate stomach discomfort in patients undergoing cancer treatment, managing liver diseases, or coping with other severe medical conditions and treatment-related complications.^{[1][2][3]}

Since 1989, PPIs like omeprazole have been vital in treating acid-related conditions. They work by forming covalent bonds with the H(+)-K(+)-adenosine triphosphatase, effectively stopping the release of H(+) ions in parietal cells. This class includes omeprazole, esomeprazole, lansoprazole, dexlansoprazole, pantoprazole, and rabeprazole, all FDA-approved as of 2015.^[4]

Histamine-2 Receptor Antagonists (H2RAs) reduce gastric acid secretion by competitively binding to H2 receptors on gastric parietal cells, blocking the effects of histamine. Normally, histamine released post-meal binds to these receptors, activating adenylate cyclase, increasing cAMP levels, and activating protein kinase A (PKA). PKA phosphorylates proteins, promoting H+/K+ ATPase transport to the plasma membrane, leading to acid secretion. H2RAs inhibit this process, suppressing both stimulated and basal acid secretion.^[5] Three H2RAs are FDA-approved in the U.S. famotidine, cimetidine, and nizatidine. Famotidine and cimetidine are available OTC or by prescription, depending on dose, while nizatidine is prescription-only. Ranitidine was previously available but withdrawn in the U.S. and suspended in Europe and Australia due to carcinogen contamination during manufacturing.^[6]

PPIs should be used as first-choice gastroprotection medications, according to clinical guidelines that are backed by systematic reviews and meta-analyses. However, no thorough comparison of PPIs and H2RAs' efficacy in treating peptic ulcers that are resistant to treatment or refractory has been conducted yet.^[9]

The population, major outcomes, and design of each reviewed article varied. Nonetheless, a typical component of every article was the efficacy of PPIs in treating ulcers and their impact on ulcer-related symptoms.

The table below provides a summary of this (Table-1)

Table 1: Different studies with study design along with GI medicines, Dosages, and their effect on different GI diseases sideways with their adverse effects

Author and Year	Country	Study Design	PPI and H2ra Prescribed with Dose	Type of GI Diseases	Distribution of Drugs in Population	Results	Adverse Effects
Chun-Sick Eom et al 2007 ^[7]	Korea	Randomized controlled trials	Pantoprazole 20, 40mg Omeprazole 20 mg Esomeprazole 20, 40mg Lansoprazole 15,30mg Rabeprazole 20mg Ranitidine 300mg Cimetidine 200mg	—	—	Proton pump inhibitor and histamine2 receptor antagonist use were significantly positively correlated with pneumonia risk, according to meta-analyses of observational studies using the two categories of acid-suppressive drugs.	Compared to controls, individuals on histamine 2 receptor antagonists had a greater rate of pneumonia.
Lauristen et al 1988 ^[8]	Denmark	Randomized double-blind comparative trial	Omeprazole 10, 20 mg	Symptomatic and Duodenal Ulcer	Omeprazole 10: 64 patients, Omeprazole 20mg: 65 patients	Omeprazole 20 mg treated 33% of patients at three weeks, whereas Omeprazole 10 mg cured 32% at four weeks.	Patient receiving 20 mg of omeprazole three days a week experienced itching and metallic taste, while another patient receiving 10 mg of omeprazole daily experienced backache, diarrhoea, indigestion, and pneumonia.
Scally B et al 2018 ^[9]	United Kingdom	Meta-analysis of randomised trials	—	Endoscopic ulcer and Duodenal ulcer	—	PPI was 84% successful in treating stomach ulcers and 87% successful in treating duodenal ulcers. For stomach and duodenal	Myocardial infarction, bone fracture, hypomagnesaemia, food poisoning, bacterial gut infection, dementia, and chronic renal

						ulcers, H2RA blockers were 78% and 76% effective, respectively.	disease have all been linked to PPI.
Miner Jr et al 2003 ^[10]	United States	Randomized, open-label, comparative five-way crossover study	Esomeprazole 40 mg, Lansoprazole 30 mg, Omeprazole 20 mg, Pantoprazole 40 mg, and Rabeprazole 20 mg	Gastroesophageal reflux disease	Esomeprazole: 34, Lansoprazole: 34, Omeprazole: 34, Pantoprazole: 34, Rabeprazole: 34	In individuals with symptoms of gastro-oesophageal reflux disease, omeprazole at the normal dose of 40 mg once day was more successful than conventional doses of lansoprazole, omeprazole, pantoprazole, and rabeprazole at controlling gastric acid at steady state.	Two of the four major adverse events led to study withdrawal, but none were thought to be treatment-related. Due to nausea, a nonserious side event, a third patient withdrew. The most common adverse event kinds were headache, nausea, diarrhoea, flatulence, or abdominal discomfort, and these were comparable to those that had been previously documented.
Chiba NA et al 1997 ^[11]	Canada	Meta analysis: Double Blind Randomized study	Pantoprazole 40mg Omeprazole 40mg Lansoprazole 30, 60mg, Ranitidine 150, 300mg Cimetidine 400mg	Esophagitis, Heartburn	—	The mean overall healing proportion was higher with PPIs (PPIs; 83.6%±11.4%) than with H2receptor antagonists (H2RA; 51.9%±17.1%), regardless of drug dosage or treatment period (≤12 weeks).	—
Liu P et al 2020 ^[13]	United Kingdom	Case control study	Esomeprazole 40 mg, Rabeprazole 40 mg Omeprazole 40mg lansoprazole 30 mg Pantoprazole 40mg	GORD Gastric-adenocarcinoma Oesophagitis Peptic ulcer	Omeprazole: 402 users, Lansoprazole: 358 users, Cimetidine: 186 users, Ranitidine: 263 users	—	Use of PPI was associated with a 45% increase in the risk of gastric cancer (unadjusted OR = 1.45, 95% CI 1.25, 1.68). Similarly, H2RA use was associated with an increase in the risk of gastric

			Ranitidine 300mg Cimetidine 200mg				cancer (fully adjusted OR = 1.44, 95% CI 1.16, 1.80, see Table 3). Similar associations were observed in stratified analysis by sex (fully adjusted OR = 1.43, 95% CI 1.05, 1.94 in men, and fully adjusted OR = 1.45, 95% CI 1.04, 2.01 in women, respectively).
Poly TN et al 2019 [24]	Taiwan	Meta analysis	Omeprazole Pantoprazole Rabeprazole Lansoprazole Esomeprazole	gastroesophageal reflux disease (GERD) and peptic ulcer disease	—	—	Patients with PPIs had a greater risk of hip fracture than those without PPI therapy (RR 1.20, 95% CI 1.14–1.28, $p < 0.0001$). An increased association was also observed in both low and medium doses of PPI taken and hip fracture risk (RR 1.17, 95% CI 1.05–1.29, $p = 0.002$; RR 1.28, 95% CI 1.14–1.44, $p < 0.0001$), but it appeared to be even greater among the patients with higher dose (RR 1.30, 95% CI 1.20–1.40, $p < 0.0001$).

The table presents a comparative analysis of various studies conducted across different countries to evaluate the effectiveness, dosages, and adverse effects of Proton Pump Inhibitors (PPIs) and Histamine-2 Receptor Antagonists (H2RAs) in treating gastrointestinal (GI) diseases. The studies include diverse study designs such as meta-analyses, randomized controlled trials, double-blind comparative trials, and case control studies.

Across the studies, PPIs consistently demonstrated superior efficacy in healing GI conditions, including gastroduodenal ulcers, GERD, and esophagitis, compared to H2RAs. For instance, Scally et al. (2018) reported an 84-87% success rate for PPIs in treating ulcers, significantly higher than the 76-78% effectiveness of H2RAs. Similarly, Chiba et al. (1997) highlighted a healing rate of 83.6% for PPIs versus 51.9% for H2RAs.

Chronic PPI use was associated with significant risks, including calcium and vitamin B12 malabsorption, enteric infections (e.g., *Clostridium difficile*), and systemic conditions like dementia and chronic kidney disease. Notable study-specific side effects included pneumonia (Chun-Sick Eom et al.), bone fractures (Tack et al.), and backache (Lauristen et al.).

Multiple studies revealed differences among PPIs in terms of acid suppression and healing rates. For example, Miner Jr et al. (2003) found Esomeprazole at 40 mg to be more effective in controlling GERD symptoms compared to other PPIs like Lansoprazole and Pantoprazole.

Liu P et al. (2020, UK) identified a significant association between PPI/H2RA use and an increased risk of gastric cancer, with adjusted odds ratios of 1.45 and 1.44, respectively. This risk was consistent across genders and was studied in patients with conditions like GORD, oesophagitis, and peptic ulcers.

Poly TN et al. (2019, Taiwan) demonstrated a dose-dependent relationship between PPI use and hip fracture risk, with the relative risk rising from low (RR 1.17) to high doses (RR 1.30). The study focused on GERD and peptic ulcer patients and included commonly prescribed PPIs such as omeprazole, pantoprazole, and esomeprazole.

While PPIs exhibit superior efficacy in GI disease management compared to H2RAs, their long-term use warrants caution due to potential adverse effects. The studies collectively emphasize the need for careful selection of therapy based on individual patient risk factors and disease profiles.

CLINICAL EFFICACY

Peptic Ulcer Disease:

- PPIs are more effective than H2RAs in healing gastroduodenal ulcers.
- A study Systematic review by Begg M et al, comparing the safety and efficacy of PPIs and H2RAs in various ulcer locations (gastric, duodenal, and pre-pyloric) and the effect of prolonging the treatment with the same medication or changing into a drug from another class in treatment-resistant ulcers, which showed key factor in ulcer healing is maintaining stomach pH for 18 to 20 hours. PPIs are the most effective inhibitors of gastric acid secretion, directly blocking the pump and consistently maintaining gastric pH above four for 15 to 22 hours daily, compared to only four hours with H2RAs.^[3]
- A Comprehensive review by Strand et al. examine the pharmacokinetics and pharmacodynamics of PPI drugs and provide an update on both the clinical use of and remaining challenges with PPIs this study confirms that acid suppression therapy remains the primary treatment for gastric and duodenal ulcers.^[4]
- A meta-analysis by Chun-Sick Eom et al. reviewed approximately 30 double-blind prospective trials comparing omeprazole (20 mg) to H2RAs, finding a therapeutic gain of 15.2% in duodenal ulcer healing ($p < 0.001$) and 9.9% in gastric ulcer healing ($p < 0.05$) after two weeks of treatment.^[7]
- Randomized double-blind comparative trial by Lauristen et al, aim of the present double-blind, comparative, randomized, placebo-controlled trial was to ascertain whether omeprazole, 20 mg 3 days a week and 10 mg daily for 6 months, was effective in preventing relapse in patients with duodenal ulcer disease. Study involving 195 patients, omeprazole 20 mg given for a week significantly reduced the incidence of recurrent duodenal ulcers compared to placebo, from 67% to 23% ($p < 0.001$).^[8]
- Another Randomized trial study by Scally et al, aimed to examine the effects of proton-pump inhibitors (PPIs), prostaglandin analogues, and histamine-2 receptor antagonists (H2RAs) in different clinical circumstances by doing meta-analyses of tabular data from all relevant unconfounded randomized trials of gastroprotectant drugs which found that PPIs were 84% effective in treating gastric ulcers and 87% effective in treating duodenal ulcers, while H2RAs were 78% effective in treating gastric ulcers and 76% effective in treating duodenal ulcers, demonstrating the superior efficacy of PPIs compared to H2RAs.^[9]

Gastro-esophageal reflux disease (GERD):

- A Meta analysis study by Chiba NA et al, which aimed to compare different classes by expressing the speed of healing and symptom relief through an approach. PPIs offer superior pH control over H2RAs over a 24-hour period. Omeprazole, OME-IR, rabeprazole, pantoprazole, and lansoprazole provide similar intragastric pH control (11–13 hours with $\text{pH} > 4$), but esomeprazole at a 40 mg daily dose offers a slightly longer duration of control.^[10]
- Dextlansoprazole with dual-release technology maintains $\text{pH} > 4$ for up to 17 hours with once-daily administration.
- A large meta-analysis study by Chiba NA et al, which aimed to compare different classes by expressing the speed of healing and symptom relief through an approach that revealed PPIs are superior in healing all grades of erosive esophagitis and providing heartburn relief compared to H2RAs, sucralfate, or placebo. The mean overall healing percentage, regardless of drug dose or treatment duration (≤ 12 weeks), was highest with PPIs ($83.6 \pm 11.4\%$) compared to H2RAs ($51.9 \pm 17.1\%$), sucralfate ($39.2 \pm 22.4\%$), or placebo ($28.2 \pm 15.6\%$). The mean heartburn-free proportion of patients was also highest with PPIs ($77.4 \pm 10.4\%$) versus H2RAs ($47.6 \pm 15.5\%$), and PPIs exhibited a significantly faster healing rate (11.7% per week) compared to H2RAs (5.9% per week) and placebo (2.9% per week).^[11] Although PPIs may not achieve complete symptom relief for all patients, they are more effective than H2RAs in improving symptoms.^[11]

SAFETY PATTERNS

- Acid suppression can lead to elevated blood gastrin levels, potentially causing enterochromaffin cell hyperplasia and gastric carcinoid formation. PPIs and H2RAs reduce the acidity of gastric secretions, leading to hypochlorhydria, which may cause bacterial overgrowth in the gut, impaired

nutrient absorption, and reduced protection against infections.^[13] Additionally, PPI use may interact with *H. pylori*, resulting in enhanced acid suppression and subsequent bacterial overgrowth, increasing the risk of gastritis and gastric cancer.^{[14][15]}

- Observational studies have explored the link between PPI use and gastric cancer risk, with a recent meta-analysis indicating a 150% increase in gastric cancer risk with long-term PPI use.^[16] Similarly, H2RA use has been associated with a 40% increase in gastric cancer risk.^[17]
- While both PPIs and H2RAs are effective for acid-related conditions, prolonged PPI use is more frequently linked to an increased risk of colorectal cancer (CRC), inflammatory bowel disease (IBD), pneumonia, and enteric infections like *Clostridium difficile*. H2RAs are generally considered a safer alternative.
- Concerns have been raised about the impact of long-term PPI use on the gut microbiome, leading to changes in the abundance and diversity of microbial species. Disruption of the gut microbiome can increase disease risk or worsen existing conditions. A study analyzing 16S rRNA gene sequences from three independent cohorts in the Netherlands found that PPI use was associated with decreased bacterial richness and significant changes in 20% of gut bacteria, including potentially pathogenic species such as *Enterococcus*, *Streptococcus*, *Staphylococcus*, and *Escherichia coli*. These alterations align with those predisposing individuals to *C. difficile* infections, potentially explaining the increased risk of enteric infections in PPI users.^[18]
- Recent Research shows that PPI usage has a more significant impact on disrupting the gut microbiota compared to H2RAs, inducing a higher degree of oral-to-gut transmission and promoting the presence of oral species in the gut. This can increase the growth rate of specific gut microbes, potentially influenced by the drug. Notably, several transmitted species have been linked to various diseases, suggesting a connection between PPI-induced microbiome changes and disease susceptibilities. For example, the detection of *F. nucleatum*, a known CRC biomarker, only in the PPI group raises concerns about its role in disease risk. Overall, PPI-induced markers are associated with more diseases than those induced by H2RAs.^[1]
- Inhibition of gastric acid secretion by PPIs can reduce calcium absorption, potentially leading to osteoporotic fractures, which are associated with increased mortality, hospitalizations, healthcare costs, and reduced quality of life.
- Both men and women using PPIs face a significantly higher risk of osteoporotic fractures, especially with use extending beyond one year (adjusted OR: 1.42) and regular use in the past year (adjusted OR: 1.37). The risk of osteoporotic fractures increases with the duration and regularity of PPI use. Reducing the duration or avoiding PPIs in favor of H2RAs may lower the risk of osteoporotic fractures in older adults.^[2]

ADVERSE EFFECTS

Proton Pump Inhibitors -PPI:

- PPIs effectively treat gastrointestinal disorders by suppressing acid production, but their long-term use poses risks. These include increased bone fracture risk, renal complications like acute interstitial nephritis and chronic kidney disease, and potential vitamin B12 deficiency leading to neurological and hematological problems. PPIs may also elevate the risk of gastrointestinal infections like *Clostridium difficile* due to changes in gut flora. Careful monitoring is crucial, especially with prolonged therapy, to mitigate these adverse effects while maintaining effectiveness.
- **Hypomagnesemia:** Although rare, PPIs can lower magnesium levels to a degree that cannot be easily corrected with supplementation and requires discontinuation of the PPI. Hypomagnesemia is a serious condition that can lead to tetany, seizures, muscle weakness, delirium, and cardiac arrhythmias. The exact cause is unclear, but it may involve decreased active intestinal absorption of magnesium by transient receptor potential channels (TRPM 6/7), which are stimulated by extracellular protons.
- **Infection:** PPIs are associated with an increased risk of *Clostridium difficile* infections, other enteric foodborne infections, and potentially a higher risk of community-acquired pneumonia. The exact mechanism is unclear, but one hypothesis is that the reduced acidity in the stomach due to PPIs leads to bacterial overgrowth and a higher risk of bacterial aspiration.
- **Rebound Acid Secretion:** PPIs can elevate gastrin levels, leading to the proliferation of enterochromaffin-like (ECL) cells, which produce histamine. Histamine typically stimulates parietal cells to activate H⁺/K⁺ ATPase, increasing acid production in the stomach. Since PPIs act downstream of histamine, this side effect does not negate their efficacy. However, discontinuation of PPIs after prolonged use can result in higher acid levels than before PPI initiation, a phenomenon known as "rebound acid secretion."
- **Vitamin B12 Deficiency:** Vitamin B12 binds to a protein called R-factor in the stomach. To release vitamin B12 from R-factor, proteases need to be activated by an acidic environment. Once freed, vitamin B12 can bind to intrinsic factor for absorption in the terminal ileum. PPIs disrupt the stomach's acidic environment, potentially leading to a vitamin B12 deficiency, although this deficiency is clinically rare.^{[19][20][21]}
- **Chronic Kidney Disease (CKD):** Evidence suggests that prolonged PPI use is linked to a higher risk of CKD.^[22] Patients with established CKD may experience faster disease progression when on PPI therapy. The primary mechanism leading to kidney damage from PPI use is believed to be acute interstitial nephritis. More than half of the patients with PPI-induced acute interstitial nephritis do not fully recover, suggesting that PPIs may cause CKD by progressing from acute interstitial nephritis with inflammatory infiltrates and edema to chronic interstitial scarring and tubular atrophy. These findings provide strong evidence that PPIs can cause acute interstitial nephritis and suggest they may also increase CKD risk.^[23]

- **Fracture Risk:** While data are conflicting, some retrospective studies indicate a dose-dependent relationship between PPI use and decreased bone mineral density, leading to an increased risk of fractures, particularly hip fractures. The risk is higher in patients with osteoporosis risk factors, such as renal dysfunction.^[24] Proposed mechanisms linking long-term PPI use with decreased bone mineral density include hypochlorhydria-associated calcium malabsorption, gastrin-induced parathyroid hyperplasia, and inhibition of bone resorption by blocking local H⁺/K⁺ ATPase.
- **Dementia:** Chronic PPI use has been linked to brain dysfunction. Neurological side effects, such as headaches, dizziness, and vertigo, have been reported with PPIs like lansoprazole, esomeprazole, and pantoprazole. Less common side effects include depression, diplopia, sleep disturbances, nervousness, tremor, sensory and perceptual abnormalities (e.g., hallucinations), and delirium. These effects may be due to PPIs' influence on ionic pumps controlling neuronal membrane potential. PPIs appear to reduce lysosomal acidity, potentially impairing the degradation of amyloid-beta protein, which accumulates in Alzheimer's disease.
- **Cardiovascular Disease:** Long-term or high-dose PPI treatment has been correlated with an increased risk of major cardiovascular events, including myocardial infarction and stroke. There is also a theoretical risk of malignant ventricular arrhythmias due to PPI-induced hypomagnesemia, which can prolong the QT interval and lead to torsade de pointes. Additionally, PPIs impair the antiplatelet effect of clopidogrel by competing for the cytochrome P450 isoenzyme CYP2C19.^[25]
- **Ranitidine-Induced Cancer:** In 2019, the FDA identified N-nitrosodimethylamine (NDMA) in ranitidine samples, leading to public warnings about potential cancer risks. NDMA levels in ranitidine were found to increase under normal storage conditions and significantly under higher temperatures, as well as over time. In April 2020, the FDA announced the withdrawal of ranitidine from the market and advised consumers to stop using it. NDMA is a potent carcinogen in experimental animals and a probable human carcinogen.^[6] A study by Gerald McGwin showed a positive association between ranitidine and pancreatic cancer, while Habel et al. found a 2.4-fold increased risk of gastric/esophageal cancer with ranitidine use.^[26]

Histamine-2 Receptor Antagonists (H2RAs)

H2RAs are generally well-tolerated with fewer severe long-term adverse effects compared to PPIs. However, they are not entirely devoid of side effects. Common adverse effects include headache, dizziness, constipation, and diarrhea. In rare instances, serious conditions such as bradycardia, mental confusion (especially in the elderly), and hepatotoxicity may occur. Long-term use can lead to tolerance, diminishing their effectiveness over time. Despite lower risk of severe adverse effects, monitoring for potential side effects is essential, and therapy adjustments may be necessary.

- **Tolerance and Side Effects:** H2 receptor antagonists are generally well-tolerated, with mild side effects that may include headache, drowsiness, fatigue, abdominal pain, constipation, or diarrhea.^[27]
- **Central Nervous System Effects:** In patients with renal or hepatic impairment, or those over 50 years old, H2RAs have been associated with central nervous system side effects such as delirium, confusion, hallucinations, or slurred speech. Cimetidine is most frequently associated with these symptoms, though famotidine can also cause similar effects.^[28]
- **Drug Interactions:** H2RAs can interact with other drugs. By increasing gastric pH, they can alter the absorption of drugs that require an acidic environment. Cimetidine, a potent inhibitor of cytochrome P450 (CYP450) enzymes, should be avoided with medications metabolized by CYP450, such as theophylline, SSRIs, and warfarin. Prolonged, high doses of cimetidine have been linked to gynecomastia, reduced sperm count, and impotence in men, as well as galactorrhea in women. These conditions typically resolve upon discontinuation of the drug. Due to these issues, clinicians often avoid recommending cimetidine for gastric symptoms.^[29]
- **Tachyphylaxis:** Regular use of H2RAs can lead to tachyphylaxis or tolerance, reducing their effectiveness as maintenance therapy for GERD. Tolerance can develop within 7 to 14 days of continuous treatment. Intermittent or as-needed use of H2RAs may help prevent the development of tachyphylaxis.^[30]
- **Infection Risk:** Compared to proton pump inhibitors, H2RAs pose a lower risk for developing bacterial overgrowth and infections.^[31]

COST CONSIDERATIONS

The cost of proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs) is an important factor in treatment decisions for gastrointestinal disorders. While both classes of drugs are effective, there are notable differences in their costs. PPIs tend to be more expensive upfront compared to H2RAs. However, their superior efficacy and longer duration of action may translate to potential cost savings in the long term by reducing the need for additional medical interventions or hospitalizations.

H2RAs are initially cheaper than PPIs but may require additional doses or medications over time, potentially negating the cost advantage. Healthcare providers and patients should weigh both upfront costs and long-term implications to optimize treatment decisions for gastrointestinal disorders.

- **Cost-Effectiveness of PPI vs. H2RA:** In studies comparing the cost-effectiveness of PPIs and H2RAs for long-term management of NSAID-induced heartburn, one study found that while PPIs are safer for patients on NSAIDs for more than three months, they are also more expensive than H2RAs. Specifically, co-therapy with traditional NSAIDs (tNSAIDs) and H2RAs is the least costly approach, whereas tNSAID and PPI co-therapy is the most expensive. The mean expected cost for tNSAID and PPI therapy is \$249.71 for a 0.4988 QALY gain, compared to \$149.82 for tNSAID and H2RA therapy for a 0.4982 QALY gain. The incremental cost-effectiveness ratio (ICER) analysis concluded that if decision-makers are willing

to pay up to \$174,788.60 per additional QALY, the optimal strategy is tNSAID and H2RA. If they are willing to pay more than this amount, tNSAID and PPI becomes the optimal strategy.^{[32][33]}

- **Cost-Effectiveness of NSAID and PPI Co-Therapy:** Another study by de Groot et al. showed that NSAID and PPI co-therapy was the most cost-effective treatment for patients, particularly those with chronic arthritis, regardless of their risk for gastrointestinal complications. This reinforces the cost-effectiveness of PPI therapy in managing gastrointestinal risks associated with long-term NSAID use.^[34]

Table 2: Comparative Analysis of PPIs vs. H2RAs in Gastrointestinal Therapy: Efficacy, Safety, and Cost

Aspect	Proton Pump Inhibitors (PPIs)	Histamine-2 Receptor Antagonists (H2RAs)
Efficacy	Superior acid suppression	Moderate acid suppression
	Longer duration of action	Shorter duration of action
	Effective in severe GERD and erosive esophagitis	Less effective in severe cases
	Higher rates of symptom relief	Lower rates of symptom relief
Safety	Generally well-tolerated	Generally well-tolerated
	Increased risk of long-term adverse effects:	Lower incidence of severe adverse effects
	- Bone fractures	
	- Renal disease	
	- Vitamin B12 deficiency	
Economic Considerations	Higher upfront cost	Lower upfront cost
	Potentially lower long-term healthcare costs	Potential for higher long-term healthcare costs
	Reduced need for further medical interventions	Higher likelihood of additional treatments
Clinical Recommendations	Best for severe conditions requiring potent acid suppression	Suitable for milder conditions requiring moderate acid suppression
	Consider individual patient risk factors	Consider individual patient symptom profile
	Cost-effective in long-term management	Economical for short-term or mild symptom management

CONCLUSION

This review highlights differences between Proton Pump Inhibitors (PPIs) and Histamine-2 Receptor Antagonists (H2RAs) in treating gastrointestinal disorders. PPIs offer superior efficacy in acid suppression, especially for severe cases like GERD. However, long-term PPI use is linked to adverse effects like bone fractures and renal disease. H2RAs, while less potent, have a safer profile with fewer severe long-term side effects, making them suitable for patients with milder symptoms or those at risk of PPI-related complications.

Economically, although PPIs incur higher initial costs, their ability to reduce the need for additional medical interventions can lead to overall cost savings in the long-term management of gastrointestinal disorders. H2RAs, with their lower upfront costs, may be more suitable for short-term use or for patients with less severe symptoms.

Clinicians should adopt a patient-centric approach, weighing the efficacy, safety, and economic factors when choosing between PPIs and H2RAs. Personalized treatment plans that consider individual patient needs, potential risks, and cost-effectiveness are essential for optimizing therapeutic outcomes. Future research should continue to refine these strategies, ensuring that both PPIs and H2RAs are used to their full potential in gastrointestinal disorder management.

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