Print ISSN: 2321-6379
Online ISSN: 2321-595X

Review Article

Enhancing Gastroesophageal Reflux Disease Outcomes with Esomeprazole: Real-world Perspectives on Acid Suppression and Patient Compliance

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Abstract

Gastroesophageal reflux disease (GERD) is a chronic acid-related disorder that significantly impacts quality of life (QoL) and can lead to potential long-term complications if left untreated. Proton pump inhibitors (PPIs) are the cornerstone of GERD therapy, with esomeprazole, the s-isomer of omeprazole, providing enhanced pharmacokinetics and superior acid suppression. Esomeprazole achieves greater plasma drug exposure, prolonged intragastric pH control, and reduced interindividual variability compared to other PPIs. These characteristics result in faster symptom relief and higher mucosal healing rates, particularly in moderate-to-severe esophagitis. Esomeprazole has shown superior efficacy in acid control and relief of reflux symptoms compared to pantoprazole, lansoprazole, and omeprazole, particularly during the initial treatment phase. It is effective across various dosing strategies, such as continuous, intermittent, and on-demand, providing clinical utility in special populations, including those with hepatic impairment or post-transplant immunosuppression. However, long-term use carries risks such as fractures, infections, and nutrient malabsorption, highlighting the importance of appropriate patient selection and monitoring. Correct administration, typically 30–60 min before meals, is essential for optimal efficacy; incorrect timing can reduce therapeutic outcomes. Patient adherence remains a critical factor in treatment success. Studies suggest that older age is associated with better adherence; however, younger patients and those with lower health literacy may require further counseling. Esomeprazole stands out as a highly effective and well-tolerated PPI, providing consistent acid suppression, rapid symptom control, and improvements in QoL. With proper dosing and sustained adherence, it represents a preferred option for managing GERD and related acid-peptic disorders across diverse patient groups.

Key words: Dosing strategy, Esomeprazole, Gastroesophageal reflux disease, Intragastric pH control, Patient adherence, Proton pump inhibitors, Reflux esophagitis

INTRODUCTION

Gastroesophageal reflux disease (GERD) typically presents with classic symptoms such as heartburn, regurgitation, and epigastric pain. A chronic condition can significantly affect quality of life (QoL) if not properly managed. Many adults with GERD report having experienced similar symptoms during childhood, suggesting early onset and long-term persistence. Adults with GERD may develop Barrett's esophagus, erosive esophagitis, or possibly esophageal cancer if treatment is not received. Children with GERD are also more likely to develop respiratory issues such as asthma and sinusitis. Effective management usually involves lifestyle modifications and long-term use of acid-suppressive therapy, particularly proton pump inhibitors (PPIs).[1]

Access this article online

IJSS
www.ijss-sn.com

Month of Submission	: 06-2025
Month of Peer Review	: 07-2025
Month of Acceptance	: 08-2025
Month of Publishing	: 08-2025

At present, PPIs are the preferred treatment for managing GERD in adults and are increasingly being recommended as

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the first-line therapy for pediatric patients aged 1–17 years.[1] Over the past 25 years, PPIs have transformed the treatment of gastric acid-related disorders. They effectively address therapeutic needs such as healing, preventing peptic ulcers, and managing GERD. Their application has now been extended to include any condition in which gastric acid is a key factor. Depending on the diagnosis, PPIs are used for short- or long-term treatment, with dosing strategies that may be continuous, intermittent, or on demand.[2]

PPIs are key agents in managing acid-related disorders such as peptic ulcer disease and GERD. They work by inhibiting the H^+/K^+-adenosine triphosphatase enzyme (proton pump) in gastric parietal cells, effectively reducing acid secretion.[3] Omeprazole was the first PPI introduced for clinical use, and esomeprazole, its (S)-isomer, was developed to enhance pharmacokinetics and acid suppression.[4] Esomeprazole is highly protein-bound, has high chiral stability, and undergoes minimal conversion to its R-isomer. Its absorption is reduced with high-fat meals, so it is best taken 30 min–1 h before eating. Compared to omeprazole, esomeprazole achieves greater plasma drug exposure due to lower first-pass metabolism and systemic clearance. It is mainly metabolized by CYP2C19 and CYP3A4, with no dose adjustment needed in the elderly or those with renal or mild hepatic impairment. However, a reduced dose is recommended in severe liver dysfunction.[4]

PHARMACOKINETICS AND PHARMACODYNAMICS

Esomeprazole exhibits time- and dose-dependent pharmacokinetics, with a significant increase in systemic exposure (area under the curve [AUC]) over the first 5 days of administration.[5] Notably, the increase in AUC for esomeprazole 20 mg was 111%, compared to 49% for an equivalent dose of omeprazole.[6] This enhanced exposure is primarily attributed to decreased systemic elimination and increased bioavailability, resulting from reduced first-pass metabolism.[6] The difference can be explained by the variations in metabolic pathways between the two isomers. Esomeprazole is predominantly metabolized through CYP3A4, whereas omeprazole (mainly the R-isomer) is largely metabolized through CYP2C19. As a result, esomeprazole lowers plasma concentrations of the hydroxy metabolite (CYP2C19-derived) while increasing levels of the sulfone metabolite (CYP3A4-derived).[7]

Pharmacodynamically, esomeprazole has a robust and steady correlation between its acid-inhibitory action and AUC, which a sigmoid Emax model may effectively describe. Esomeprazole 20 mg, when administered as a solution, inhibited stimulated gastric acid output by approximately 90%, compared to 79% with omeprazole 20 mg given in capsule form. Additional studies have confirmed this trend, showing esomeprazole achieving 91% inhibition compared to 64% with omeprazole after repeated 15 mg dosing. The enhanced acid suppression observed with esomeprazole is not solely attributable to increased systemic exposure AUC; rather, with repeated dosing, its antisecretory effect intensifies due to the irreversible binding of the active sulfenamide metabolite to newly synthesized proton pumps over time, resulting in a cumulative and prolonged inhibitory action. These findings highlight the superior pharmacokinetic profile and enhanced pharmacodynamic response of esomeprazole compared to omeprazole.[6]

CLINICAL EFFICACY

In a meta-analysis, esomeprazole, the active enantiomer of omeprazole, demonstrated superior efficacy in healing erosive esophagitis at 8 weeks, particularly at the 40 mg dose. Although the difference compared to omeprazole was statistically significant, the clinical advantage was modest. Esomeprazole 20 mg did not show a significant benefit at 4 weeks, indicating limited short-term efficacy. Its advantage was more evident in patients with moderate-to-severe esophagitis. In *Helicobacter pylori* (*H. pylori*) eradication regimens, esomeprazole 40 mg showed some benefit, although results were variable and affected by heterogeneity.[8]

In a study by Sugimoto and Furuta, esomeprazole demonstrated high efficacy in the treatment of acid-related diseases in Japanese populations. A 24-week course of esomeprazole 20 mg daily achieved a 92.0% healing rate in patients with GERD. Furthermore, it effectively prevented peptic ulcer development in 96.0% of patients receiving non-steroidal anti-inflammatory drugs. The enhanced clinical outcomes were attributed to esomeprazole's strong acid suppression and favorable pharmacokinetics, particularly with the lower impact of CYP2C19 polymorphisms common in Japanese individuals.[9] Esomeprazole has minimal interactions with most CYP enzymes but may mildly affect drugs metabolized by CYP2C19 (e.g., diazepam and phenytoin). It does not significantly impact CYP3A4 substrates, although clarithromycin may increase esomeprazole levels without clinical concern. Its acid suppression can alter the absorption of pH-sensitive drugs such as digoxin and ketoconazole.[10]

Safety Profile of Esomeprazole in Long-Term Management

Esomeprazole is generally well-tolerated but long-term use, especially in the elderly, raises safety concerns. Chronic use has been associated with an increased risk of fractures due to impaired calcium absorption and possible effects on bone metabolism. High-dose or prolonged PPI therapy (>1 year) should be avoided in patients with risk factors such as osteoporosis, and supplementation with calcium and vitamin D may be considered.[11]

PPIs also increase the risk of certain infections, including *Clostridium difficile*, enteric infections, and possibly pneumonia, particularly shortly after starting therapy.[12] In patients with cirrhosis, PPI use has been associated with a higher risk of spontaneous bacterial peritonitis. Therefore, PPIs should be used judiciously in high-risk groups.[13]

Nutrient malabsorption is another concern. Long-term PPI use can lead to vitamin B12 deficiency and hypomagnesemia, especially in the elderly or those on medications such as diuretics.[11,14] It may also reduce the absorption of drugs such as thyroxine, necessitating dose adjustments.[11]

Chronic PPI use may increase the incidence of stomach cancer and atrophic gastritis in patients with *H. pylori* infection. *H. pylori* eradication is recommended before starting long-term therapy in high-prevalence regions.[11]

Esomeprazole Versus Other PPIs: Efficacy in Gastric Acid Control

Esomeprazole maintained intragastric pH above 4.0 for the longest duration over 24 h and had a significantly higher proportion of patients with pH >4 for more than 12 h. Pantoprazole consistently showed the lowest efficacy, whereas no significant differences were observed among omeprazole, lansoprazole, and rabeprazole. These findings are consistent with previous studies showing superior acid control with esomeprazole on days 1 and 5 of therapy.[15] In a study by Miner *et al.*, esomeprazole maintained pH >4 for 58.4% of the day, which aligns with other reports ranging from 57.7% to 69.8%. This consistent performance is likely due to esomeprazole's favorable pharmacokinetics and reduced interpatient variability.[16] Figure 1 represents the percentage of patients achieving sustained intragastric pH ≥ 4 for ≥12 and ≥16 h over 24 h after 5 days of once-daily treatment with esomeprazole 40 mg versus omeprazole 40 mg.[15]

Esomeprazole in Patients with Liver and Kidney Disease

In patients with mild-to-moderate hepatic impairment, esomeprazole metabolism may be reduced. In cases of severe hepatic impairment, this reduction is more pronounced. Consequently, 20 mg/day is the highest dosage that is advised for these people. With once-daily dosage, esomeprazole and the primary metabolites usually do not accumulate significantly.[17]

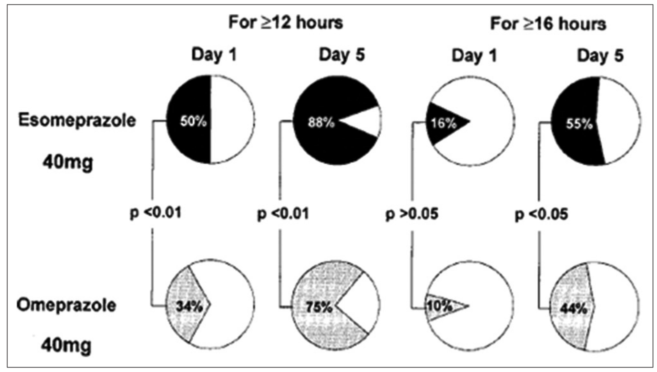

Figure 1: Percentage of patients achieving sustained intragastric pH ≥4 for ≥12 and ≥16 h over 24 h after 5 days of once-daily treatment with esomeprazole 40 mg versus omeprazole 40 mg

In a level 4, multiple-dose, pharmacokinetic study, esomeprazole exposure in patients with Child–Turcotte–Pugh (CTP) class A and B cirrhosis was similar to that in healthy individuals. Drug exposure, however, more than doubled in CTP C patients. As a result, official product information advises limiting esomeprazole dosage to a maximum of 20 mg/day in patients with CTP C. Safety data are limited-one study reported adverse events (constipation, diarrhea, and hepatic encephalopathy) in 25% of patients with cirrhosis receiving 40 mg daily for 5 days, with the encephalopathy occurring in a patient with severe cirrhosis. Expert consensus, based on limited evidence, classifies esomeprazole as having no known additional risk in cirrhosis but supports dose reduction in CTP C due to increased drug exposure.[17]

In a randomized clinical trial by El-Bohy *et al.,* the role of esomeprazole in stable kidney transplant recipients was evaluated over 6 months. Patients receiving esomeprazole 40 mg once daily showed a significant reduction in serum creatinine levels, indicating improved or maintained graft function, whereas those on pantoprazole remained stable. Crucially, neither group experienced any instances of rejection. Esomeprazole was also associated with lower cyclosporine trough levels compared to pantoprazole, suggesting a reduced potential for drug accumulation and interaction. This makes esomeprazole a preferable option for transplant recipients on cyclosporine-based immunosuppression. However, like all PPIs, it carries a risk of hypomagnesemia, which is particularly relevant in transplant patients.[18]

Use of Esomeprazole in Patients with GERD

Esomeprazole has been shown to significantly improve health-related QoL in patients with GERD, including those with non-erosive GERD, erosive GERD, and Barrett's esophagus, all of whom experience similar impairments in QoL.[19] A large uncontrolled study by Kulig *et al.*, involving

6,215 patients, demonstrated that esomeprazole (20 mg for non-erosive GERD and 40 mg for erosive GERD) led to rapid improvement in GERD symptoms and QoL after just 2 weeks of treatment.[19,20] Another randomized study by Pace *et al.*, involving 6,017 patients, compared continuous esomeprazole 20 mg daily with on-demand use over 6 months. Both regimens significantly improved QoL, but the continuous regimen showed superior maintenance of QoL gains.[19,21] In addition, a Norwegian study by Hansen *et al.,* compared continuous esomeprazole (20 mg), on-demand esomeprazole (20 mg), and continuous ranitidine (150 mg twice daily) over 6 months. Both esomeprazole regimens were more effective than ranitidine in all QoL domains, with continuous esomeprazole showing better outcomes and higher patient satisfaction.[19,22]

Correct versus Incorrect PPI Dosing and Its Effect on GERD Symptoms

A study evaluating PPI dosing habits in 638 newly treated patients with GERD found that correct and optimal dosing were poorly followed in the primary care setting. Only 27% of patients were using their PPIs correctly (i.e., with meals or up to 60 min before meals), and just 9.7% dosed optimally (15–60 min before the first meal of the day). Incorrect dosing included taking more than 60 min before or after meals, at bedtime, or on an as-needed basis. Despite suboptimal dosing practices, GERD symptom severity, measured using the QoL in Reflux and Dyspepsia questionnaire, did not show statistically significant differences between correct and incorrect dosers. However, patients with severe symptoms tended to be incorrect dosers, suggesting that improper dosing may contribute to poor symptom control in this subgroup.[23]

Impact of Age and Gender on Adherence to PPI Treatment

Several survey-based studies have explored the factors that influence adherence to PPI therapy in patients with GERD. A consistent finding across multiple studies is that older patients tend to be more adherent to PPI therapy than younger ones. For instance, in a U.S.-based study, the average age of adherent patients was 50.5 years compared to 47.2 years for non-adherent individuals ($P < 0.001$). Similarly, observation from another study found that Austrian patients who were adherent had an average age of 58.2 years, significantly higher than the 44.7 years observed in non-adherent individuals ($P < 0.05$). VanAnother clinical study also reported a marginal increase in adherence with increasing age. However, the evidence on the impact of gender on adherence was mixed. Kamolz *et al.* found that women were significantly more likely to report adherence than men (60% vs. 24.3%; $P < 0.05$), whereas a national claims database study found that women were less likely to be adherent than men, with an adjusted odds ratio of 0.89 (95% confidence interval: 0.86–0.93). This study used the medication ownership ratio to assess adherence, calculated based on the percentage of patients continuing their initial PPI prescription at 3-month intervals over 1 year.[24]

Esomeprazole versus Other PPIs in Reflux Symptom Relief

In a randomized controlled trial by Zheng involving 274 patients with endoscopically confirmed reflux esophagitis, daily morning doses of omeprazole 20 mg, lansoprazole 30 mg, pantoprazole 40 mg, and esomeprazole 40 mg were compared over 8 weeks. Although endoscopic healing rates were similar across all 4 PPIs at 8 weeks, esomeprazole provided significantly faster relief of heartburn in the initial week. Patients receiving esomeprazole experienced a more rapid decrease in mean heartburn scores, with complete symptom resolution by day 5, compared to other groups. Thus, esomeprazole stands out for its ability to expedite symptom relief, making it a preferred option for patients seeking faster improvement in reflux esophagitis.[25]

CONCLUSION

Esomeprazole has emerged as a leading PPI due to its enhanced pharmacokinetic and pharmacodynamic properties. Its high systemic bioavailability, prolonged acid suppression, and reduced interindividual variability contribute to superior symptom control and mucosal healing, particularly in moderate-to-severe GERD.

Esomeprazole continuously exhibits more efficient and long-lasting intragastric pH regulation among the available PPIs, keeping pH >4 for extended periods of time. This contributes to more rapid relief of reflux symptoms, especially heartburn, often outperforming other PPIs in early treatment phases.

Effective management of GERD requires not only the selection of the right agent but also its correct use. Esomeprazole should be administered 30–60 min before meals to optimize proton pump inhibition. Incorrect timing, such as taking it after meals or at bedtime, reduces acid suppression and may compromise clinical outcomes. Education about proper dosing is essential.

Adherence is another key determinant influencing therapeutic success. Studies show that older patients tend to be more adherent, whereas younger individuals and those with lower health literacy may benefit from targeted counseling. Simplifying regimens, emphasizing timing, and addressing misconceptions can enhance compliance and improve long-term disease control.

Esomeprazole offers flexible dosing strategies such as continuous, intermittent, or on-demand, based on disease severity and patient preference. Continuous therapy tends to provide the most durable symptom relief and QoL improvements. Its safety and efficacy in special populations, including patients with liver impairment or post-transplant immunosuppression, further support its clinical utility.

In conclusion, esomeprazole fulfils key criteria for optimal GERD therapy, including rapid symptom resolution, effective gastric acid control, durable mucosal healing, and a favorable safety profile. Correct use and consistent adherence are critical to maximizing therapeutic outcomes, making esomeprazole a preferred option in both general and high-risk patient populations.

EXPERT OPINION

Clinical Estimate of the Percentage of Irregular or Incorrect PPI Use in GERD

Most healthcare professionals (HCPs) (43.15%) reported that between 30 and 40% of GERD patients take PPIs incorrectly or irregularly. In addition, 32.63% of HCPs believed that the proportion could be as high as 50%, 15.26% estimated it to be between 20% and 30%, and 8.90% reported it to be 10–20%. These findings highlighted widespread adherence issues. Simplified dosing and better patient education may help improve outcomes. Figure 2 represents the graphical representation of the clinical estimate of the percentage of irregular or incorrect PPI use in GERD.

Recommendations to Prevent Incorrect PPI Use in Patients with GERD

The majority of HCPs (57.90%) recommended a comprehensive approach to prevent incorrect administration of PPIs, selecting "All of the above," which includes considering patient symptoms and preferences, understanding food interactions based on drug formulation, and timing flexibility for most PPIs except pantoprazole. About 31.58% emphasized the importance of aligning PPI administration with individual patient needs and dosing preferences. A smaller proportion (4.73%) highlighted the role of food-drug interactions, whereas 2.11% stated that timing (morning or evening) is generally flexible except for pantoprazole. Furthermore, 3.16% supported both patient preference and food interaction considerations, and 0.52% endorsed preference along with timing flexibility. These insights highlight the need for personalized and informed prescribing to enhance the effectiveness of PPI therapy.

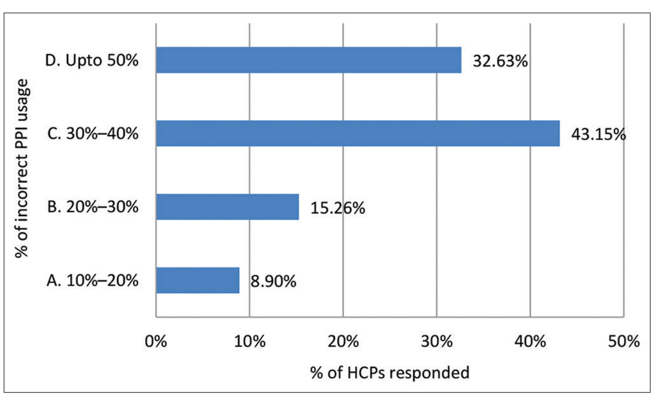

Figure 2: Clinical estimate of percentage of irregular or incorrect proton pump inhibitor uses in gastroesophageal reflux disease

Impact of Dosing Frequency on Adherence to PPI Treatment

A significant majority of HCPs (86.84%) agreed that frequent dosing is a major factor affecting patient adherence to PPI therapy. They noted that complex dosing schedules can reduce compliance, particularly in patients on multiple medications. In contrast, 12.63% of HCPs disagreed, possibly attributing non-adherence to other factors such as side effects or lack of symptom relief. A small proportion (0.52%) did not provide any response. These insights emphasize the value of once-daily PPI regimens to enhance adherence and treatment success.

Ideal PPI Properties for Effective GERD Management: Physician Perspectives

Most HCPs (56.84%) identified once-daily dosing as the most ideal feature for effective GERD management, citing its potential to improve adherence and simplify treatment. In addition, 31.58% emphasized the importance of maintaining intragastric pH >4 for extended periods, recognizing its role in symptom control and mucosal healing. A smaller group (3.68%) prioritized consistent bioavailability regardless of food intake, which ensures reliable drug absorption. Interestingly, 7.89% of respondents did not consider any of these properties as ideal, possibly indicating other clinical priorities or preferences. These responses demonstrate a multifactorial approach to optimal GERD therapy, with dosing simplicity taking precedence.

Esomeprazole OD Advantages Over Pantoprazole in Enhancing Adherence

A substantial majority of HCPs (71.58%) responded that all the listed properties of esomeprazole once-daily dosing-flexibility to take it in the morning or evening, and consistent gastric acid inhibition regardless of food intake-contribute to improved patient adherence compared to pantoprazole. Furthermore, 2.11% listed dosing flexibility and 1.58% mentioned food-independent acid inhibition as important features, while 24.73% specifically attributed improved adherence to once-daily dosing. The benefits of esomeprazole in improving adherence are graphically represented in Figure 3.

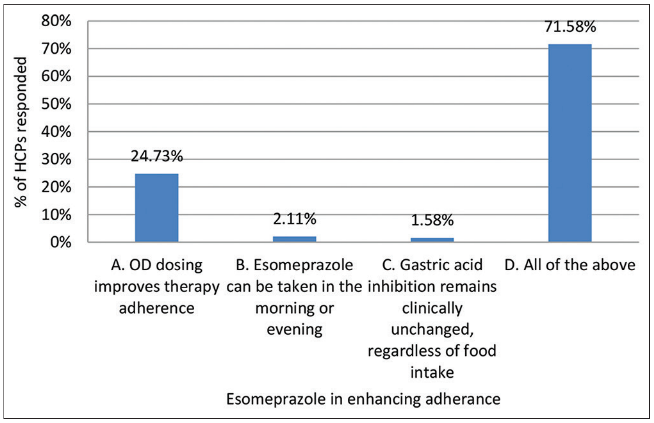

Figure 3: Esomeprazole once daily advantageous over pantoprazole in enhancing adherence

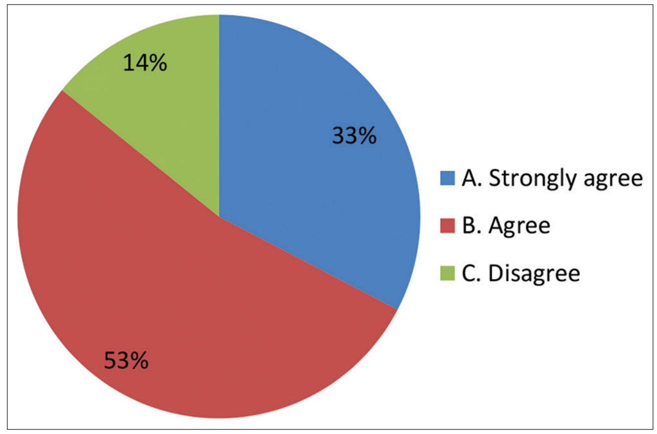

Figure 4: Effect of postprandial esomeprazole administration on reflux symptom control

Superior 24-h Acid Control with Esomeprazole versus Pantoprazole

The majority of HCPs (99.47%) agreed that esomeprazole offers more effective and sustained gastric acid control over 24 h compared to pantoprazole. This suggests strong clinical confidence in the ability of esomeprazole to maintain consistent acid suppression throughout the day and night, which may contribute to better symptom relief and treatment outcomes in patients with GERD. Only 0.52% of HCPs disagreed with this view.

Effect of Postprandial Esomeprazole Administration on Reflux Symptom Control

With 53.16% of HCPs agreeing and 32.63% strongly agreeing, the majority of them felt that postprandial esomeprazole delivery does not exacerbate reflux symptoms. This indicates a broad clinical consensus that esomeprazole maintains its therapeutic efficacy even when taken after meals, offering flexibility in dosing without compromising symptom control. However, 14.21% of HCPs disagreed, suggesting that a subset of clinicians may still prefer pre-meal administration to ensure optimal effectiveness in certain patients. The effect of postprandial esomeprazole treatment on managing reflux symptoms is graphically depicted in Figure 4.

Comparative Efficacy of Esomeprazole 40 mg OD in Sustained Acid Suppression

When compared to typical dosages of other regularly used PPIs, such as lansoprazole, omeprazole, pantoprazole, and rabeprazole, a large proportion of HCPs (95.78%) agreed that esomeprazole OD 40 mg is more effective in managing gastric acid levels at steady state in patients with GERD. This strong consensus demonstrates clinical confidence in esomeprazole's superior pharmacological profile and acid-suppressive capacity, which may result in improved symptom control and therapeutic outcomes. Only a small proportion of HCPs (4.21%) disagreed with this opinion.

Symptom-guided Adjustment of Esomeprazole Timing and Dosage in GERD Management

The majority of HCPs supported the approach of adjusting the timing and dosage of esomeprazole based on particular GERD patient symptom patterns, with 53.68% agreeing and 44.21% strongly agreeing. This indicates a significant clinical preference for individualized treatment plans to attain the best possible acid suppression. Only 2.11% of HCPs disagreed with this approach.

Esomeprazole Over Pantoprazole: A Clinical Choice

A large majority of HCPs (67.37%) preferred esomeprazole over pantoprazole due to its comprehensive benefits, including effective post-meal acid control, flexibility of anytime PPI dosing, improved patient adherence, and 24-h symptom relief. A significant proportion (18.42%) emphasized esomeprazole's ability to provide sustained acid suppression throughout the day. In addition, (5.26%) few HCPs highlighted improved adherence as the primary reason, whereas others (5.26%) valued both adherence and 24-h relief. Very few HCPs (0.52% each) selected either effectiveness after meals alone or in combination with 24-h relief. A small percentage (2.63%) preferred esomeprazole due to its dosing flexibility. These responses indicate that esomeprazole's broad clinical advantages, particularly its efficacy and convenience, contribute significantly to its preference among HCPs managing GERD.

HCPs prefer esomeprazole over pantoprazole due to its superior acid control, flexible dosing, and better adherence, supporting its use across varied GERD patient profiles.

ACKNOWLEDGMENT

We would like to acknowledge Scientimed Solutions Pvt. Ltd. for assistance in developing the manuscript.

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How to cite this article: Rajesh K, Goyal N, Agarwal N, Tongaonkar A. Enhancing Gastroesophageal Reflux Disease Outcomes with Esomeprazole: Real-world Perspectives on Acid Suppression and Patient Compliance. Int J Sci Stud 2025;13(5):14-20.

Source of Support: Nil, **Conflicts of Interest:** None declared.