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Original Article

From Twice-daily to Once-daily: Indian Expert Opinion on Overcoming Nocturnal Acid Breakthrough in Gastroesophageal Reflux Disease Management

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Abstract

Background: Gastroesophageal reflux disease (GERD) remains a prevalent disorder worldwide, and incomplete acid control despite proton pump inhibitor (PPI) therapy continues to challenge clinicians. Nocturnal acid breakthrough (NAB) and variable adherence to twice-daily (BID) regimens often contribute to persistent symptoms. This expert opinion study assessed clinicians' perceptions regarding the efficacy and practicality of current PPI regimens, with particular focus on Pantoprazole and Esomeprazole.

Methods: A cross-sectional, questionnaire-based survey was conducted among 95 clinicians across India in June–July 2024. The 10-item questionnaire explored expert opinions on nocturnal acid buildup, PPI failure, NAB prevalence, comparative effectiveness of Esomeprazole versus Pantoprazole, and the impact of once-daily (OD) dosing on adherence. Descriptive statistics and Pearson's Chi-square test ($P < 0.05$) were used for analysis.

Results: A majority of clinicians (90%) agreed that nocturnal acid buildup is a major concern in GERD. The leading perceived cause of PPI failure was inadequate 24-h acid control (51%), followed by poor compliance with BID regimens (23%). Around 74% reported persistent symptoms despite Pantoprazole 40 mg BID, whereas 58% estimated NAB occurrence in 30–60% of patients. Most experts (89%) agreed that Esomeprazole 40 mg OD provides superior 24-h acid suppression, and 91% preferred switching to OD therapy to improve adherence.

Conclusion: Clinicians widely recognize NAB and adherence barriers as key determinants of suboptimal GERD control. Esomeprazole 40 mg OD is perceived as offering stronger, sustained acid suppression and better patient compliance, aligning with pharmacodynamic and consensus guideline evidence supporting individualized, OD PPI therapy for effective round-the-clock reflux management.

Key words: Esomeprazole, Gastroesophageal reflux disease, Nocturnal acid breakthrough, Proton pump inhibitors, Treatment adherence

INTRODUCTION

Gastro-esophageal reflux disease (GERD) is one of the most prevalent and burdensome disorders of the upper gastrointestinal tract.[1] Characterised by retrograde movement of gastric contents into the oesophagus, GERD manifests clinically through symptoms such as heartburn, regurgitation, chest pain, and sleep disturbances.[1] Epidemiological studies estimate a global prevalence of 4.16–22.4% depending on region and diagnostic criteria.[2] The primary therapeutic goal in GERD is the suppression of gastric acid secretion to maintain the intragastric pH above the mucosal injury threshold, typically pH 4, thereby reducing oesophageal acid exposure and allowing mucosal healing.[3]

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Despite effective daytime control, many patients continue to experience reflux symptoms at night. This phenomenon, known as nocturnal acid breakthrough (NAB), refers to a fall in intragastric pH below 4 for more than 1 h during the night in patients receiving proton pump inhibitors (PPIs).[4] NAB has been reported in a large proportion of treated GERD patients and is linked with nocturnal symptoms, sleep disruption, and mucosal damage.[5]

In a crossover pH-metric study comparing esomeprazole and pantoprazole, Miehlke and colleagues observed that at night, esomeprazole maintained intragastric pH above 4 for 85.4% of the time, compared with 63.6% for pantoprazole ($P = 0.0001$), and episodes of NAB were less common with esomeprazole.[6] Such evidence highlights that NAB is not merely a physiological curiosity but a clinically significant gap in acid suppression that can explain residual night-time symptoms in patients otherwise compliant with therapy. Maintenance of intragastric pH above 4 throughout the 24-h cycle remains the principal pharmacodynamic target of PPI therapy, as emphasised by Röhss and colleagues.[7]

Despite advances in acid-suppressive therapy, many GERD patients continue to experience nocturnal symptoms and incomplete acid control. Expert clinical insight is essential to understand real-world treatment challenges such as NAB, suboptimal PPI response, and adherence barriers. Gathering clinician perspectives helps bridge the gap between controlled pharmacodynamic data and everyday therapeutic outcomes, guiding more effective GERD management strategies.

PPI Pharmacology and Inter-drug Differences

PPIs act by irreversible inhibition of the gastric H^+/K^+-ATPase proton pump.[8] Although members of the class share a similar mechanism, they differ in stereochemistry, metabolic stability, and systemic bioavailability, which in turn affect the consistency and duration of acid suppression. Esomeprazole, the S-isomer of omeprazole, was developed to improve pharmacokinetic predictability and achieve more prolonged suppression relative to racemic omeprazole and other PPIs.[9]

A comparative pharmacodynamic trial reported that esomeprazole 40 mg delivers superior acid suppression in a higher proportion of patients and sustains intragastric pH above 4 for a longer duration than lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg, or rabeprazole 20 mg.[7]

This superior pH control has been confirmed in additional head-to-head comparisons. Hatlebakk noted that Esomeprazole results in a higher median 24-h intragastric pH and a longer duration with pH levels above 4 compared with standard doses of other PPIs.[10]

Such pharmacodynamic advantages translate into improved symptom relief and mucosal healing. In a prospective clinical comparison, Srikanth *et al.* found that patients treated with esomeprazole experienced quicker healing and greater improvement in symptom scores than those receiving pantoprazole.[11]

Collectively, these studies demonstrate that esomeprazole yields more sustained 24-h acid suppression, including superior night-time control, thereby lowering the likelihood of NAB and persistent symptoms.

Persistence of Symptoms and Treatment Failure despite PPI Therapy

Even with adequate PPI dosing, approximately 30–40% of GERD patients continue to experience symptoms such as heartburn, regurgitation, or nocturnal discomfort. Multiple mechanisms underlie this apparent "treatment failure," including rapid drug metabolism, functional heartburn, weakly acidic reflux, and most importantly, poor adherence to prescribed regimens.[12]

Dal-Paz *et al.* investigated adherence patterns in a Brazilian tertiary-care setting and concluded that among GERD patients seen at a tertiary care center, adherence to prescribed PPI therapy was low, which may have contributed to treatment failure.[13]

Similarly, Dickman *et al.* compared PPI responders and non-responders and found that treatment failure with PPIs, whether taken once or twice daily, is strongly linked to poor adherence when compared with patients who respond to therapy.[14]

These findings underscore the behavioral dimension of pharmacologic efficacy: Even the most potent inhibitor cannot work if not taken correctly. Twice-daily regimens, while sometimes necessary, are especially prone to missed doses, highlighting the clinical appeal of once-daily (OD) formulations with longer duration of action.

The Challenge of Adherence and Rationale for OD Therapy

Adherence to chronic therapy is a major determinant of outcome in GERD management. A OD regimen not only simplifies dosing but can enhance persistence and regularity. Upadhyay *et al.* noted that in India, pantoprazole is the PPI most commonly prescribed by healthcare professionals. However, the standard 40 mg dose often falls short for patients with extraesophageal symptoms, partial response, concurrent NSAID use, or more severe disease in those who are overweight or obese. Current guidelines

recommend dose escalation, typically through twice-daily therapy, but this can negatively affect adherence.[15]

Given that adherence failures amplify the apparent incidence of PPI resistance, simplifying regimens is a pragmatic strategy. Pharmacokinetic and pharmacodynamic data support the clinical feasibility of effective OD dosing with potent agents such as esomeprazole. Hatlebakk summarized that the steady and predictable pharmacokinetics of esomeprazole support OD dosing that does not depend on meal timing.[10]

Thus, both biological potency and regimen simplicity are essential for achieving sustained acid suppression in real-world settings.

In clinical practice, the management of residual symptoms often follows a stepwise approach: Confirm adherence and timing, exclude functional heartburn, and consider switching to a more potent PPI or adjusting the dosing schedule. Esomeprazole's pharmacological profile – higher systemic bioavailability (~90%), stereoselective metabolism, and prolonged acid suppression – allows OD use to achieve levels of control comparable or superior to twice-daily dosing with less potent agents.[16] As summarized by Hatlebakk that esomeprazole provides more effective acid suppression and symptom relief with OD dosing and has the most consistent pharmacokinetic profile among PPIs.[10]

Broader Pharmacotherapeutic Perspective

While PPIs remain the mainstay of GERD treatment, awareness of limitations such as NAB, incomplete symptom resolution, and adherence barriers informs current clinical guidelines. Addressing these challenges may involve optimising PPI selection, dosing time, and formulation. Esomeprazole's consistent 24-h coverage supports its role as a first-line therapy where nocturnal control and convenience are priorities. The interplay between pharmacology and patient behavior highlights that efficacy in practice depends as much on human factors as on molecular potency.[17]

Thus, GERD remains a major clinical and economic burden, and effective 24-h acid suppression, especially at night, is key to lasting symptom relief and mucosal healing. Esomeprazole offers stronger and more consistent intragastric pH control than pantoprazole and other PPIs, resulting in better nocturnal acid suppression and improved healing. However, treatment success also depends on adherence, with OD dosing offering an advantage over more complex regimens. With its combination of potent pharmacologic effect and simple dosing, esomeprazole is well-positioned as a preferred therapy for GERD. Further research on adherence, dosing strategies, and residual symptoms will continue to optimize outcomes for patients.

MATERIALS AND METHODS

A cross-sectional, multiple-response questionnaire-based study was conducted among clinicians specializing in the management of GERD across major cities in India. Invitations were extended to practicing gastroenterologists, internal medicine specialists, and general physicians with substantial experience in treating GERD. The study was conducted in June–July 2025, and a total of 95 clinicians from different Indian states voluntarily participated. Clinicians who declined participation or returned incomplete forms were excluded from the analysis.

A structured 10-item expert opinion questionnaire was developed based on current literature and consensus guidelines, including the Association of Physicians of India (API) and the Indian Society of Gastroenterology (ISG) Consensus (Bhatia *et al.*, 2020), and validated studies comparing various PPIs.[5,11,18] The questionnaire focused on key aspects of GERD management, such as NAB, persistence of symptoms despite PPI therapy, comparative efficacy of esomeprazole versus pantoprazole, and treatment adherence patterns. Participants were instructed to complete the form independently and were requested not to consult peers to avoid response bias. Written informed consent was obtained from all participants before study initiation, and confidentiality of individual responses was maintained.

Statistical Methods

Descriptive statistics were used for data analysis. Categorical variables were presented as percentages, with frequency and percentage distributions provided for each variable. Pie and bar charts were generated using Excel 2013.

RESULTS AND DISCUSSION

The results of the survey, consisting of 10 closed-ended questions, addressed key clinical domains in the management of GERD. These domains included: (1) The perceived clinical relevance of nocturnal acid buildup; (2) common causes of PPI treatment failure; (3) residual nocturnal symptoms and NAB despite pantoprazole therapy; (4) comparative 24-h acid suppression and symptom control with esomeprazole versus pantoprazole; and (5) treatment adherence and dosing regimen preferences, are discussed below.

Q1 – Nighttime Acid Buildup is a Major Concern for Patients with GERD

A large majority of clinicians, 67% strongly agreed, and 23% agreed, that night-time acid buildup is a significant

issue for GERD patients. This mirrors epidemiologic data showing that up to 70% of GERD patients experience nocturnal symptoms associated with sleep disturbance and reduced quality of life.[18] Nocturnal symptoms are common and have important sequelae. The API-ISG consensus notes that nocturnal symptoms in GERD are common and are accompanied by sleep disturbance, and a large telephone survey found high rates of night-time heartburn and associated sleep disturbance. Pharmacodynamically, maintaining intragastric pH >4 over the 24-h period is an accepted therapeutic target because tissue injury and reflux symptoms are strongly pH-dependent.[7] If clinicians identify nighttime acid as important, that justifies attention to nighttime acid control strategies such as choice of PPI, timing, bed-head elevation, and lifestyle advice.

Q2 – Common Reasons for PPI Treatment Failure (Options: Poor Compliance with BID Regimen/Nocturnal Acid Burn/Inability to Provide 24-h Gastric Acid Control/Other)

When asked to identify common reasons for PPI treatment failure, 51% cited inability to provide 24-h acid control, 23% cited poor compliance with BID regimens, 16% pointed to nocturnal acid burn, and 11% selected other causes [Figure 1]. This pattern aligns with the dual-etiology concept, pharmacodynamic insufficiency and behavioral non-adherence, as major contributors to incomplete response. Multiple studies highlight both contributors. Adherence is a major driver of apparent therapeutic failure: Dal-Paz *et al.* found that patients with GERD exhibited a high rate of low adherence to the prescribed PPI therapy, which may play a role in the therapy failure.[13] Dickman *et al.* similarly linked PPI failure to lower adherence and more complex disease features, and PPI failure appears to be significantly associated with compliance as compared with PPI responders.[14]

At the same time, pharmacodynamic gaps (insufficient 24-h pH control, NAB) are real. Comparative pH studies demonstrate that some PPIs (for example, esomeprazole) maintain pH >4 longer than others, which may explain the persistence of nocturnal symptoms despite adherence in some patients.[7] Thus, clinicians should assess both adherence (dose timing, missed doses) and objective acid exposure (pH/impedance) when symptoms persist; management may include adherence counseling, switching PPI, dosing schedule changes, or investigation (24-h pH) for refractory cases.

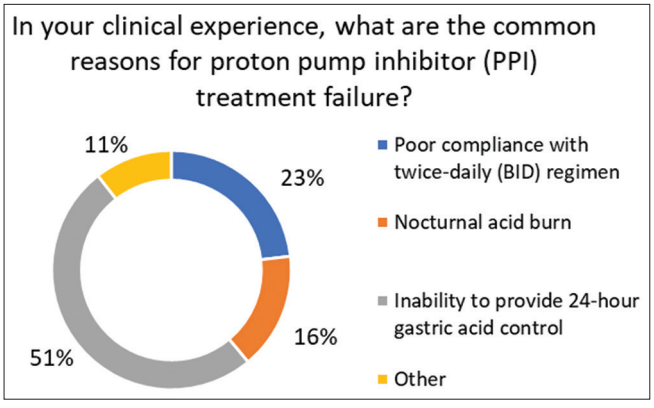

Figure 1: Clinician's insight on common reasons for proton pump inhibitor treatment failure

Q3 – Persistent Heartburn and Nocturnal Acid Reflux despite Pantoprazole 40 mg BID

Overall, 74% of clinicians (34% strongly agree + 40% agree) reported that patients often experience persistent heartburn and nocturnal reflux despite pantoprazole 40 mg BID. Head-to-head pharmacodynamic data indicate differential night-time pH control among PPIs. In a randomised crossover trial, esomeprazole produced superior night-time pH control compared to pantoprazole: "During night-time the proportion of time with intragastric pH >4 was 85.4% with esomeprazole and 63.6% with pantoprazole ($P = 0.0001$). Also, NAB occurred less frequently on esomeprazole.[6] Other studies and reviews support esomeprazole's greater ability to maintain intragastric pH >4 for long durations, which can translate into fewer nocturnal breakthroughs versus pantoprazole.[7,10]

Q4 – Approximately What Percentage of Patients Report NAB While Receiving Pantoprazole? (Options e.g., 10–30%, 30–60%, >60%)

When estimating NAB frequency among their patients on pantoprazole, 58% of experts reported 30–60%, 22% reported 10–30%, and 20% >60% [Figure 2]. These figures closely resemble pH-monitoring data.

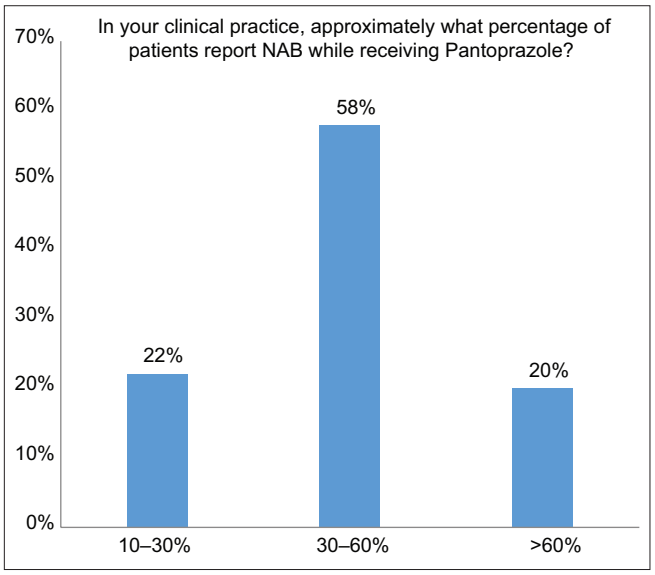

Figure 2: Clinicians' responses on the percentage of patients reporting nocturnal acid breakthrough while receiving Pantoprazole

In the Miehlke crossover study, NAB was observed less frequently on esomeprazole, with a reported numerical difference (example figures quoted in that trial include NAB rates of ~15% for esomeprazole versus ~42% for pantoprazole in certain cohorts). Those absolute percentages illustrate that NAB on pantoprazole is not rare.[6] This aligns with published pharmacodynamic data and supports evaluating alternative regimens for night-time control.

Q5 – Pantoprazole 40 mg BID is Unable to Maintain an Intragastric pH above 4 for Even 12 h in About Half of the Patients (Opinion Item)

A combined 68% of respondents (26% strongly agree + 42% agree) believed pantoprazole 40 mg BID fails to maintain pH >4 for even 12 h in about half of patients. Quantitative pH comparisons show pantoprazole achieves less time with pH >4 than esomeprazole (example: Intragastric pH >4 was maintained 21.1 h with esomeprazole versus 16.8 h with pantoprazole in one study). While 16.8 h is >12 h, population heterogeneity and interindividual variability mean a notable minority may have much shorter durations on pantoprazole.[6,7] This implies that clinicians should recognize inter-individual variability in acid control with pantoprazole; if many patients have inadequate pH coverage, consider a pharmacologic switch or dosing adjustment. The majority opinion that pantoprazole fails to sustain pH control in half of patients reflects the known pharmacodynamic variability and supports considering more potent, longer-acting PPIs for comprehensive 24-h coverage.

Q6 – Esomeprazole 40 mg OD Provides Effective 24-h Acid Suppression, Potentially Enhancing Adherence and Improving Outcomes Compared to Pantoprazole BID

Around 89% of clinicians (57% strongly agree + 32% agree) endorsed esomeprazole 40 mg OD as providing effective 24-h suppression and better adherence than pantoprazole BID. Comparative trials show esomeprazole provides more sustained pH control than several other PPIs, and reviews propose that esomeprazole's pharmacokinetics (stereoselective S-isomer, higher bioavailability) yield more predictable acid suppression. Esomeprazole 40 mg provides greater acid control and maintains an intragastric pH >4 for a longer period.[7]

Adherence evidence: Several observational studies and surveys report suboptimal adherence in routine care; simplifying dosing to OD tends to improve real-world adherence for chronic medications in general (and some studies suggest similar benefits in acid-suppression therapy), though the magnitude varies. Dal-Paz *et al.* documented low adherence as a contributor to therapeutic failure.[13,19] The combination of stronger pharmacodynamic control plus simpler OD dosing can plausibly improve outcomes, but clinicians should confirm adherence and measure response, not assume drug potency alone will fix persistent symptoms.

Q7 – For Preventing NAB, an Ideal PPI Should Provide Sustained 24-h Intragastric Acid Suppression, Low NAB Incidence, High Bioavailability, and be Suitable for OD Dosing to Enhance Adherence

Most clinicians – 51% strongly agree, and 35% agree – identified sustained 24-h suppression, low NAB, high bioavailability, and OD dosing convenience as features of an ideal PPI. The evidence base supports these properties as desirable. Clinical and pharmacologic reviews emphasise achieving >16–18 h with pH >4 as clinically meaningful; esomeprazole often meets that threshold more consistently. Hatlebakk and others describe esomeprazole's more predictable pharmacokinetics and longer pH control as favorable features.[7,10] Accepting this profile directs clinicians toward PPIs with documented sustained pH control and encourages attention to dosing convenience.

Q8 – Is Esomeprazole 40 mg More Effective Than Pantoprazole 40 mg in Managing NAB and Ensuring 24-h Symptom Control? (Yes/No)

A striking 91% of experts responded Yes when asked if esomeprazole 40 mg is more effective than pantoprazole 40 mg for NAB and 24-h symptom control. This view is evidence-supported as multiple randomized and crossover pharmacodynamic trials and mechanistic reviews report that esomeprazole maintains pH >4 for a longer fraction of the 24-h cycle and reduces NAB frequency compared to pantoprazole. Example: "Intragastric pH >4 was maintained for 21.1 h with esomeprazole and 16.8 h with pantoprazole ($P < 0.0001$).[6] Clinical outcome differences (healing rates, symptom relief) are usually smaller than pharmacodynamic differences, and meta-analyses suggest modest absolute benefits of esomeprazole over other PPIs in healing rates; nonetheless, the pH data are consistent.[20] Clinical studies also demonstrate modestly higher healing rates and symptom resolution with esomeprazole.[11]

Q9 – Esomeprazole is Often Preferred due to Effectiveness When Taken after Meals, Flexibility as an "Anytime" PPI, Better Adherence and Consistent 24-h Relief

Around 90% (52% strongly agree + 38% agree) preferred esomeprazole over pantoprazole because of better post-meal efficacy, "anytime" dosing flexibility, and more consistent 24-h relief. Esomeprazole's pharmacokinetics are more predictable and, in some formulations, can be more forgiving of meal timing; review articles and pharmacology papers highlight esomeprazole's systemic bioavailability and predictable acid suppressant, in some formulations.[10]

However, the guideline position (API-ISG) emphasizes that in equipotent doses, PPIs are similar for symptom control, while acknowledging modest benefits for esomeprazole in healing; individual patient factors and adherence remain central.[18] It may also imply that clinicians who prioritize ease of dosing and predictable pH control may prefer esomeprazole; cost, availability, and guideline recommendations for equipotent dosing will also influence choice in practice.

Q10 – A Significant Number of Patients Miss Doses on BID Regimens. Do You Agree That Switching to an OD Formulation (e.g., Omeprazole 40 mg) Could Improve Adherence and Provide More Consistent, All-day Symptom Relief?

An identical 91% of clinicians agreed that converting from BID to OD formulations – such as omeprazole 40 mg – could improve adherence and provide more consistent symptom relief. Empirical data support this behavioral logic. In a Nepalese prescribing-pattern study, Basyal *et al.* found that twice-daily regimens were associated with poorer compliance compared to OD use.[21] Treatment adherence literature and GERD studies indicate missed doses are common and can explain treatment failure; Dal-Paz *et al.* have shown low adherence contributes meaningfully to poor outcomes.[13]

Simplifying dosing is a general adherence strategy. Evidence specific to switching from pantoprazole BID to an OD PPI for improved clinical outcomes is mixed – improved adherence is plausible, but the clinical benefit depends on whether the chosen OD agent provides equivalent or better 24-h acid suppression. Esomeprazole often provides stronger 24-h pH control at OD dosing compared to standard OD pantoprazole, supporting the logic of switching to an OD agent with stronger pharmacodynamics when adherence is the concern.[6,7] Thus, in case of frequent missed doses on BID regimens, switching to a OD PPI with proven 24-h coverage (e.g., esomeprazole) is an evidence-aligned strategy, paired with adherence counseling.

CONCLUSION

This survey provides a comprehensive snapshot of real-world clinical perceptions and expert opinion regarding the management of GERD in India. The findings demonstrate broad consensus among clinicians that nocturnal acid buildup remains a major unmet therapeutic need, with pantoprazole frequently failing to sustain intragastric pH above 4 despite twice-daily dosing. The majority of respondents acknowledged that esomeprazole 40 mg OD offers superior 24-h acid suppression, effectively addressing NAB and enhancing treatment adherence through simplified dosing.

Clinicians overwhelmingly associated PPI treatment failure with inadequate 24-h acid control and poor compliance, emphasising the dual importance of pharmacologic potency and behavioral adherence in GERD management. The preference for potent, OD PPIs such as esomeprazole reflects an evidence-driven shift toward optimising both efficacy and convenience to improve long-term outcomes.

In line with current consensus guidelines, the survey underscores the need for individualized therapy, focusing on patient adherence, symptom timing, and selection of PPIs capable of providing consistent, round-the-clock acid suppression. Future research should aim to integrate clinical outcomes with pharmacodynamic and adherence data to further refine GERD management strategies and minimise nocturnal symptom burden.

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