REVIEW ARTICLE

Optimizing Proton-pump Inhibitor Therapy in Patients with Comorbidities Receiving Polypharmacy Treatment: Insights from Clinical Practice in India

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Abstract

Background: The safety and efficacy of proton-pump inhibitors (PPIs) in gastroesophageal reflux disease (GERD) patients on polypharmacy is challenging to manage. Rabeprazole's unique metabolism reduces drug–drug interactions (DDI), making it beneficial for patients with polypharmacy. This study aimed to explore the safety and effectiveness of rabeprazole in Indian comorbid GERD patients on polypharmacy.

Methods: A cross-sectional survey was conducted (November, 2024 and January, 2025), which included healthcare professionals (HCPs) with experience in prescribing PPIs. The survey included 10 questions addressing issues faced in polypharmacy settings.

Results: Around 91.9% preferred prescribing rabeprazole over other PPIs in polypharmacy patients. CYP450 enzyme interactions are considered by 73.3% HCPs when prescribing PPIs, with a strong emphasis on minimizing DDI in polypharmacy contexts. Rabeprazole was chosen by a major share of HCPs for its unique nonenzymatic metabolism and minimal interaction with the cytochrome P450 system, suggesting suitability in polypharmacy patients. Furthermore, 70% HCPs suggested rabeprazole could improve cardiovascular (CV) outcomes by optimizing antiplatelet therapy, and 74.4% supported its safety in patients on antiplatelet therapy.

Conclusion: Rabeprazole appears to be the preferred PPI in managing GERD among patients on polypharmacy, primarily due to its favorable safety profile and minimal DDI, and may be advantageous in clinical practice.

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Introduction

Proton-pump inhibitors (PPIs) effectively reduce gastric acid secretion and have a strong safety profile. They are commonly used to treat esophagitis, gastric ulcers, gastroesophageal reflux disease (GERD), dyspepsia and bleeding ulcers, *Helicobacter pylori* eradication, and Zollinger–Ellison syndrome, as well as to prevent nonsteroidal anti-inflammatory drugs (NSAID)-induced gastrointestinal (GI) toxicity.[1] They are also used for stress ulcer prophylaxis and as gastroprotective agents when prescribed with NSAIDs. In India, the available PPIs include rabeprazole, pantoprazole, omeprazole, esomeprazole, lansoprazole, dexlansoprazole, dexrabeprazole, and ilaprazole.[2]

Proton-pump inhibitors, especially omeprazole, can significantly interact with drugs such as benzodiazepines, carbamazepine, diazepam, phenytoin, and theophylline, increasing their serum levels and the risk of adverse effects. They also interfere with clopidogrel metabolism, reducing its effectiveness and raising the risk of thrombotic events. Older patients on multiple medications are particularly vulnerable to these interactions, which may lead to increased morbidity, adverse events, and hospitalizations due to overprescription and polypharmacy.[1]

Proton-pump inhibitors can also impair the absorption of drugs such as tyrosine kinase inhibitors, protease inhibitors, and iron, especially when combined with oral iron supplements. They also interact with cytochrome (CYP)2C19 and CYP3A4 enzymes, potentially leading to drug interactions, with omeprazole and esomeprazole being the most likely inhibitors. Additionally, long-term PPI use can cause vitamin B12 deficiency and magnesium depletion, particularly when combined with metformin or diuretics, highlighting the need for careful monitoring in polypharmacy.[3]

Most drugs, including several PPIs and antiplatelet agents, are metabolized by CYP enzymes, particularly CYP2C19 and CYP3A4. Clopidogrel, a prodrug, relies on CYP2C19 for activation, and PPIs can compete for this enzyme, potentially inhibiting clopidogrel's antiplatelet effect and increasing the risk of cardiovascular (CV) events. In contrast, omeprazole, pantoprazole, and lansoprazole are strong inhibitors of CYP2C19, and rabeprazole has a lower inhibitory effect (Fig. 1).[4,5] Ticagrelor and prasugrel are metabolized by different CYP enzymes, avoiding this interaction.[5]

Clinical studies have shown that rabeprazole offers superior outcomes compared with other PPIs, including sustained intragastric pH >4 over 24 hours postdose, faster onset of action, and reduced nocturnal heartburn. These attributes, combined with its safer drug–drug interaction (DDI) profile, make rabeprazole an ideal candidate for managing GERD and associated symptoms, particularly in patients receiving polypharmacy treatment.[6]

Methods

Study Design

The survey was designed to explore the clinical decision-making process when prescribing PPIs, specifically rabeprazole, and the relative safety and efficacy in patients on multiple medications. This study utilized

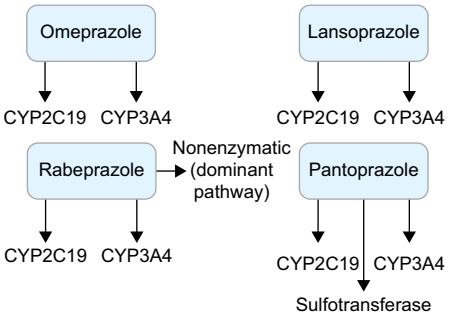

Fig. 1: Major metabolic pathways for the PPIs and the CYP450 enzymes involved

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a cross-sectional survey design to gather insights into the prescription practices of PPIs in patients receiving polypharmacy treatment and having comorbidities, with a specific focus on the use of rabeprazole.

Survey Development

The questionnaire was developed to assess the frequency of PPI prescription in polypharmacy settings, commonly observed DDIs, and factors influencing the selection of PPIs. The survey included a total of 10 questions related to prescribing patterns, PPI selection criteria, drug interactions, and clinical experiences with rabeprazole. Multiple-choice, ranking, and open-ended questions were used to gather both quantitative and qualitative data.

Participants

Clinicians with experience in prescribing PPIs, particularly for patients with multiple comorbidities, were invited to participate. The survey was distributed to healthcare professionals (HCPs), including physicians, cardiologists, and gastroenterologists, through email. Inclusion criteria required that respondents had experience prescribing PPIs, with particular emphasis on rabeprazole.

Survey Administration, Data Collection, and Analysis

The survey was conducted *via* Google Forms between November 14, 2024, and January 16, 2025, ensuring confidentiality and anonymity. After the survey, data were compiled and analyzed using Microsoft Excel. Open-ended responses were categorized to identify trends in clinical practices. Additionally, rankings of factors influencing PPI choice were analyzed to determine which aspects clinicians prioritize in polypharmacy settings.

Results

A total of 87 HCPs from various clinical settings completed the survey, and their responses were analyzed for insights.

Frequency of PPI Prescriptions

Among the 87 HCPs surveyed, 40.7% reported prescribing PPIs to >90% of their patients receiving polypharmacy treatment. Additionally, 52.3% indicated that they prescribed PPIs to 40–50% of such patients, whereas 4.7% prescribed them to 20–30% of their patients. A smaller proportion, 2.3%, reported prescribing PPIs to only 10–20% of their patients (Fig. 2).

Frequency of PPI Prescription among Patients with Comorbidities

Around 91.9% of HCPs reported prescribing rabeprazole as the most common PPI to patients with comorbidities. Pantoprazole was chosen by 6.9% of HCPs, whereas omeprazole was prescribed by only 1.2%. Lansoprazole was not reported as a commonly prescribed option. This suggests a strong preference for rabeprazole among clinicians when managing patients with multiple health conditions.

DDIs in PPI Patients with Comorbidities

According to 91.9% of the HCPs, polypharmacy can cause significant DDIs in patients with comorbidities. In contrast, 8.1% did not think that polypharmacy was a significant risk factor for drug interactions in these patient populations.

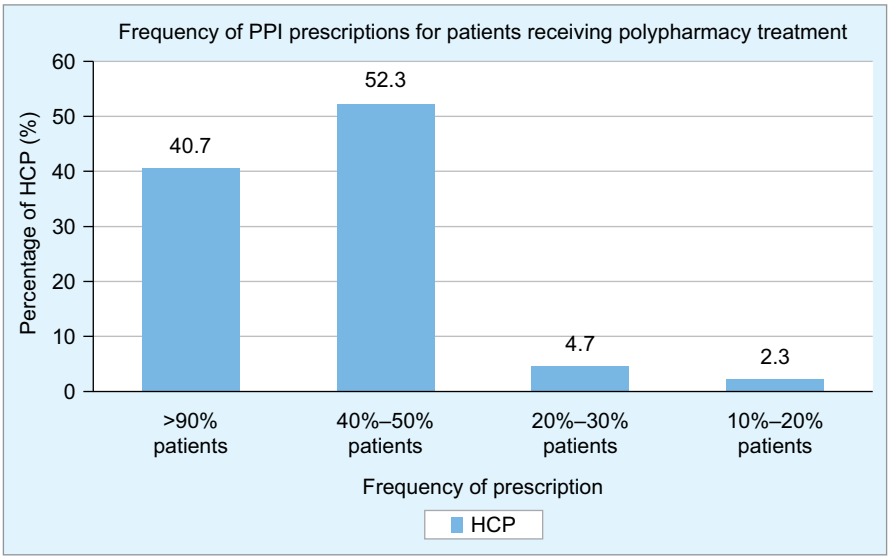

Fig. 2: Frequency of PPI prescriptions for patients receiving polypharmacy treatment

Importance of CYP450 Enzyme Interactions in Drug Prescription

Healthcare professionals recognize the role of CYP450 in drug prescription, with 73.3% considering key factors such as variability, genetics, and toxicity. A few considered interindividual variability in drug response as a major clinical issue (11.6%) and polymorphic enzymes' impact on drug metabolism (9.3%), whereas 5.8% emphasized the risks of coprescribing CYP450-metabolized drugs.

Common DDIs Considered before Prescribing PPIs in Patients Receiving Polypharmacy Treatment

Healthcare professionals prescribing PPIs to polypharmacy patients commonly take into account major DDIs, with 73.3% considering CYP2C19 and CYP3A4 metabolism effects, as well as clopidogrel inhibition. Additionally, 15.1% focus on increased serum concentrations of CYP2C19-metabolized drugs, whereas 5.8% highlight the elevated levels of CYP3A4-metabolized drugs and clopidogrel metabolism inhibition.

Common DDIs Observed in Clinical Practice, Focusing on PPIs, and Polypharmacy

In the survey, 74.4% of HCPs reported not observing any significant DDIs involving PPIs. However, 25.6% specified drug interactions, including esomeprazole with aspirin, esomeprazole with clopidogrel, omeprazole with clopidogrel, and pantoprazole with warfarin.

Factors Influencing the Choice of PPI in Patients Receiving Polypharmacy Treatment

According to HCPs, efficacy was ranked as the most important factor by 61 (70.9%) and as the second most important by 13 (15.1%). Safety profile was also a key consideration, with 55 (63.9%) placing it second and 16 (18.6%) ranking it first. Cost played a moderate role, with 45 (52.3%) ranking it third, whereas 24 (27.9%) placed it fourth. Patient preference had minimal influence as 46 (53.5%) ranked it fourth, and DDI potential was ranked as the least important factor by 44 (51.2%) (Fig. 3).

Consideration of Rabeprazole for Patients Receiving Polypharmacy Treatment

Given the unique metabolic pathway of rabeprazole, which minimizes DDIs, 97.7% of HCPs indicated that they would consider prescribing it for patients receiving polypharmacy treatment, whereas only 2.3% stated that they would not (Fig. 4).

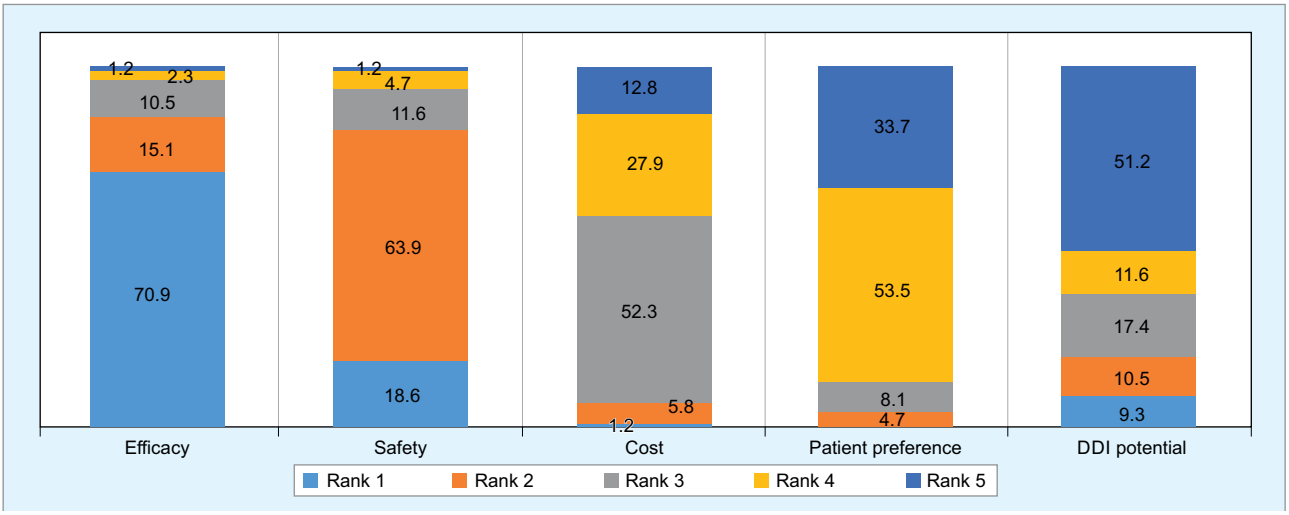

Fig. 3: Factors affecting the choice of PPI in patients with comorbid GERD receiving polypharmacy treatment

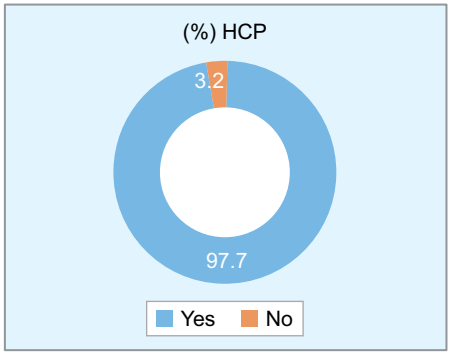

Fig. 4: Consideration of prescribing rabeprazole for patients receiving polypharmacy treatment

Opinion on Prescription of Rabeprazole in Patients with Cardiac Comorbidities

About 70% of HCPs believe that rabeprazole reduces GI complications, improves CV outcomes by optimizing antiplatelet therapy, and minimizes DDI in patients with atherosclerotic CV disease receiving polypharmacy treatment. Additionally, 21% link it to better antiplatelet compliance, whereas 4.6% see benefits in reducing statin interactions and lowering blood pressure in patients with GERD—hypertension.

Safety of Rabeprazole in Patients with Cardiovascular Disease Undergoing Antiplatelet Therapy

A majority of HCPs (74.4%) support the safety of rabeprazole in patients with CV disease on antiplatelet therapy. However, 22.1% think that rabeprazole carries a low risk of major adverse CV events (MACE) when combined with clopidogrel, whereas 2.3% of HCPs reported that rabeprazole is not associated with drug interactions with medications such as theophylline, phenytoin, warfarin, or diazepam.

Discussion

The current study found that 52% of HCPs advocate for the use of PPIs in patients receiving polypharmacy treatment. This aligns with the findings by Alhumaidi et al., who stress the use of rabeprazole instead of esomeprazole due to its potentially safer DDI profile.[7] Another study by Tan and Juurlink also highlights the need for standardizing drug interaction evaluations. While clinically significant drug interactions with PPIs are rare, their frequent use necessitates careful monitoring for any potential interactions. Effective prescribing practices, careful consideration of specific drug classes, and active pharmacist involvement are vital in mitigating risks associated with polypharmacy treatment.[3]

The survey results highlight rabeprazole as the preferred PPI for managing GERD in patients receiving polypharmacy treatment, owing to its excellent safety profile and minimal drug interaction risk. Rabeprazole offers superior acid suppression and has a lower tendency to interact with other medications, making it an ideal choice for patients requiring multiple prescriptions. It demonstrates unique selectivity for the cysteine 813/822 sites on the proton-pump, converting rapidly to its activated sulphenamide form. Furthermore, rabeprazole dissociates more quickly from H^+, K^+-ATPase than other PPIs, resulting in faster H^+, K^+-ATPase inhibition. Its minimal affinity for various CYP isoenzymes and reliance on alternate elimination pathways reduce the likelihood of DDIs.[5,8,9]

The study evaluating DDI with PPI by Ogawa and Echizen showed no significant interactions of rabeprazole with other medications (theophylline, phenytoin, warfarin, or diazepam). The pharmacokinetics of rabeprazole differ from those of other PPIs, with no notable changes observed in the area under the curve for theophylline, phenytoin, warfarin, or diazepam, regardless of the subjects' CYP2C19 genotypes. These findings suggest that rabeprazole has a minimal effect on the metabolism of these drugs, making it a safer option for patients receiving polypharmacy treatment, particularly those with comorbidities requiring multiple medications.[5,10]

In patients taking NSAIDs, approximately 25% develop peptic ulcers. A study by Mizokami showed that rabeprazole achieves a 71.1% endoscopic cure rate in treating NSAID-induced ulcers during continuous NSAID therapy.[11] Low-dose aspirin (LDA) therapy, although effective in reducing CV events by 25%, significantly increases the risk of GI complications, with the likelihood of these complications rising 2–5 times. In a long-term, randomized, multicenter trial by Fujishiro et al., rabeprazole (10 and 5 mg daily) was well tolerated and prevented the recurrence of peptic ulcers in patients on LDA therapy.[12] These findings further confirm rabeprazole's effectiveness in preventing upper GI ulcers or bleeding in patients on long-term NSAID or LDA therapy.

Interestingly, 98% of HCPs in this study recommended rabeprazole over other PPIs such as pantoprazole, omeprazole, and lansoprazole for patients with GERD receiving polypharmacy treatment, largely due to its superior drug interaction profile. Dalal et al. suggest that the benefits of PPI use in reducing GI bleeding risk outweigh the potential adverse CV effects, especially in cardiac patients. Rabeprazole, as a weak CYP2C19 inhibitor, presents a lower risk for clinically significant drug interactions, particularly in patients on dual antiplatelet therapy with clopidogrel and aspirin.

Unlike other PPIs, rabeprazole does not increase the risk of MACE when used with clopidogrel.[5]

Further, rabeprazole has been shown to prevent gastric mucosal damage induced by dual therapy with LDA and clopidogrel, as demonstrated in the study by Uotani et al. Their findings confirmed that rabeprazole significantly reduced gastric damage and hemorrhage in patients on this dual therapy. This supports the use of rabeprazole in preventing GI events in patients on LDA and clopidogrel.[13] These insights align with the survey findings, with 74% of HCPs preferring rabeprazole in patients on antiplatelet therapy due to its safer drug interaction profile. Moreover, Desai and Anand reported that rabeprazole, due to its minimal DDI potential, is the preferred choice for patients with chronic kidney disease and geriatric populations. Its low interaction risk makes it an optimal option in these vulnerable patient groups where DDIs can have significant clinical consequences.[2]

Conclusion

This study highlights the challenges and key considerations in optimizing PPI therapy for patients receiving polypharmacy treatment and having comorbidities in India. Rabeprazole has emerged as a preferred therapeutic option for managing GERD, primarily due to its unique nonenzymatic metabolic pathway, which distinguishes it from other PPIs. Its minimal interaction with the CYP system makes rabeprazole particularly suitable for patients on multiple medications, ensuring more consistent therapeutic outcomes, particularly for those with comorbid conditions requiring polypharmacy. The drug provides rapid symptom relief, sustained efficacy, and high patient satisfaction.

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