

Appropriateness of Proton Pump Inhibitor (PPI) Use in Clinical Practice: A Review Article

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ABSTRACT

Proton Pump Inhibitors (PPIs) are among the most commonly prescribed medications worldwide for the management of acid-related gastrointestinal disorders such as gastroesophageal reflux disease (GERD), peptic ulcer disease (PUD), and *Helicobacter pylori* infection. Since their introduction in the late 1980s, PPIs have transformed the management of acid-peptic disorders owing to their potent and sustained acid-suppressive action. Although PPIs are highly effective and generally safe for short-term therapy, inappropriate and prolonged use has become a major concern in modern clinical practice, with several drug-utilization studies reporting inappropriate prescription rates ranging from 50% to over 80% in both inpatient and outpatient settings, often without clear indications or documented justification. Long-term and irrational use of PPIs has been associated with adverse effects including chronic kidney disease, osteoporosis-related fractures, *Clostridium difficile* infection, community-acquired pneumonia, vitamin B12 and magnesium deficiencies, and clinically relevant drug interactions, along with increased healthcare costs. This review article evaluates the appropriateness of PPI prescribing practices across clinical settings, examines the physician-, patient-, and system-level factors that drive inappropriate utilization, discusses the evidence for associated complications, and outlines guideline-based prescribing and deprescribing strategies. Rational use of PPIs through proper clinical assessment, dose optimization, periodic therapy review, and structured deprescribing can significantly improve patient safety and reduce unnecessary economic burden on healthcare systems [1,2,3,4].

KEYWORDS

Proton Pump Inhibitors, Inappropriate Prescribing, Deprescribing, Rational Drug Use, Gastroesophageal Reflux Disease, Adverse Drug Reactions

1. INTRODUCTION

Proton Pump Inhibitors (PPIs) are potent acid-suppressive agents that act by irreversibly inhibiting the gastric H⁺/K⁺ ATPase enzyme system, commonly in gastric parietal cells. [3] They are widely used for the treatment of gastroesophageal reflux disease (GERD), peptic ulcer disease (PUD), Zollinger-Ellison syndrome, Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)-induced ulcers, and *Helicobacter pylori* eradication therapy [3,5]. Due to their high efficacy and favourable short-term safety profile, PPIs have become one of the most frequently prescribed classes of drugs globally [6].

1.1 Mechanism of Action and Pharmacokinetics

PPIs are prodrugs that require activation in the acidic environment of the parietal cell canaliculus, where they are converted to their active sulphenamide form and form a covalent, irreversible bond with cysteine residues on the H⁺/K⁺ ATPase pump [3]. This irreversible binding explains the prolonged duration of acid suppression relative to the plasma half-life of the parent drug, since restoration of acid secretion requires synthesis of new pump protein. Commonly used agents include omeprazole, esomeprazole, lansoprazole, dexlansoprazole, pantoprazole, and rabeprazole, which differ modestly in onset of action, bioavailability, and hepatic metabolism through the cytochrome P450 system, particularly

CYP2C19 and CYP3A4^[3,6]. Because PPIs act only on actively secreting proton pumps, optimal efficacy requires dosing before a meal, a detail that is frequently overlooked in clinical practice and may itself contribute to perceived treatment failure and unnecessary dose escalation.

1.2 Epidemiology of PPI Utilization

Global consumption of PPIs has risen steadily over the past two decades, driven by their availability as both prescription and over-the-counter formulations, direct-to-consumer marketing, and their broad use as gastroprotective agents alongside NSAIDs, corticosteroids, and antiplatelet therapy^[6,7]. Drug-utilization studies conducted across tertiary care hospitals in India and other countries have consistently identified PPIs among the most frequently prescribed drug classes in general medicine, surgical, and critical care units^[1,9,10,11]. This scale of use, combined with the chronic nature of acid-related disorders, means that even a modest rate of inappropriate prescribing translates into a substantial burden of unnecessary drug exposure at a population level.

Despite their therapeutic benefits, growing evidence suggests that PPIs are often prescribed inappropriately without valid clinical indications or continued for unnecessarily prolonged durations^[7,8]. Studies conducted in tertiary care hospitals have demonstrated that a substantial proportion of patients receive PPIs without proper justification, particularly during hospital discharge, where inpatient stress-ulcer prophylaxis or empirical therapy is frequently continued without reassessment^[1,4,9,10,11]. In many cases, PPIs are prescribed prophylactically without assessing individual risk factors or reviewing the necessity of therapy, reflecting a broader pattern of defensive and habitual prescribing rather than indication-based decision-making^[2,12].

Inappropriate use of PPIs contributes to polypharmacy, drug interactions, increased healthcare expenditure, and avoidable side effects. Long-term PPI therapy has been linked with complications such as chronic kidney disease, hypomagnesemia, osteoporosis-related fractures, vitamin B12 deficiency, pneumonia, and *Clostridium difficile* infection^[13,14,15,16,17,18]. Elderly patients, individuals with multiple comorbidities, and those receiving several concurrent medications are particularly vulnerable to these complications, given age-related changes in renal function, bone metabolism, and gut microbiota^[18].

Clinical guidelines recommend that PPIs should be prescribed only for approved indications and for the shortest effective duration, usually ranging from 4 to 8 weeks for most acid-related disorders.^[19,20] Step therapy approaches involving antacids or H2 receptor antagonists may be considered for mild to moderate symptoms before initiating PPIs^[21]. Regular evaluation of ongoing therapy and deprescribing strategies are essential to minimize unnecessary use, particularly in patients where the original indication for therapy is no longer present or was never clearly documented^[22].

This review article aims to analyse the appropriateness of PPI use in clinical practice, evaluate factors contributing to irrational prescribing, discuss the potential adverse outcomes of prolonged therapy, and emphasize the importance of evidence-based prescribing and structured deprescribing practices to ensure rational and safe use of PPIs across both inpatient and outpatient settings.

2. MATERIALS AND METHODS

A narrative literature search was conducted using electronic databases including PubMed, Google Scholar, and Science Direct, covering articles published between 2006 and 2025. Search terms used, either alone or in combination, included “proton pump inhibitors,” “inappropriate use,” “overprescription,” “deprescribing,” “adverse effects,” “stress ulcer prophylaxis,” and “rational prescribing.”

Original research articles, observational and drug-utilization studies, systematic reviews, meta-analyses, and clinical practice guidelines addressing the appropriateness and safety of PPI use were included. Studies conducted in adult inpatient, outpatient, and critical care settings were considered, along with clinical practice guidelines issued by relevant professional bodies. Articles not directly addressing PPI prescribing patterns, safety, or deprescribing, as well as non-English language publications and case reports without generalizable findings, were excluded.

Relevant information was extracted and organized thematically under three broad domains: the appropriateness of PPI use and factors contributing to inappropriate prescribing, adverse effects associated with long-term therapy, and strategies to promote rational prescribing and deprescribing. As a narrative rather than systematic review, no formal quality-scoring instrument was applied to included studies; findings are synthesized descriptively to provide a broad, clinically oriented overview of the topic rather than a quantitative pooled estimate of effect.

3. APPROPRIATENESS OF PPI USE

Appropriate use of PPIs involves prescribing these medications only when clinically indicated according to established guidelines and appropriateness criteria ^[19,20]. Common approved indications include GERD, erosive esophagitis, peptic ulcer disease, *H. pylori* eradication therapy, Zollinger-Ellison syndrome, and prevention of NSAID-induced gastric ulcers in high-risk patients ^[3,21].

3.1 Approved Clinical Indications

In GERD and erosive esophagitis, PPIs are considered first-line therapy, typically prescribed for 4 to 8 weeks, with maintenance therapy reserved for patients with recurrent or severe disease ^[19]. In *H. pylori* infection, PPIs form an essential component of eradication regimens, combined with two or more antibiotics for 10 to 14 days, after which continued acid suppression beyond the eradication course is not routinely required unless an underlying ulcer or complication warrants it^[3]. For NSAID- or antiplatelet-associated gastric injury, gastroprotection with a PPI is appropriate specifically in patients at elevated risk, such as those with a prior history of peptic ulcer disease, concurrent anticoagulant or corticosteroid use, advanced age, or high-dose NSAID therapy, rather than as a blanket co-prescription for all NSAID users ^[21]. Stress ulcer prophylaxis in critically ill patients is appropriate primarily in those with recognized risk factors such as mechanical ventilation beyond 48 hours, coagulopathy, traumatic brain or spinal injury, extensive burns, or multi-organ failure, and should be discontinued once these risk factors resolve or the patient is transferred out of critical care^[12].

4. MAGNITUDE AND PATTERNS OF INAPPROPRIATE USE

Several observational studies have revealed widespread overuse and inappropriate continuation of PPIs in hospitalized patients. In many instances, patients are discharged on long-term PPI therapy despite having no documented indication, most commonly because inpatient stress-ulcer prophylaxis initiated during an acute admission is carried forward into outpatient prescriptions without reassessment. Studies have reported inappropriate prescription rates ranging from 50% to 80% across general medicine, surgical, and geriatric care settings, indicating a significant gap between clinical practice and evidence-based recommendations ^[1,9,10,11,23,24,25,26]. Similar patterns of overuse have been documented at the point of hospital discharge, where PPIs initiated for non-specific gastrointestinal symptoms or as prophylaxis are frequently continued into long-term outpatient regimens without formal indication or planned review date ^[24,26].

4.1 Factors Contributing to Inappropriate Prescribing

Several interacting factors drive inappropriate PPI prescribing. At the physician level, defensive prescribing, limited consultation time, uncertainty regarding indications for stress ulcer prophylaxis, and a widespread perception that PPIs are essentially free of clinically significant risk all contribute to unnecessary initiation and continuation of therapy^[7,23]. At the systemic level, electronic prescribing systems and standardized admission order sets often include PPIs by default for hospitalized patients regardless of individual risk factors, while the absence of routine pharmacist - led medication review at discharge allows inappropriate therapy to be carried into the community largely unchecked ^[24,25]. Patient-level factors, including direct request for symptomatic relief, self-medication with over-the-counter PPIs, and reluctance to discontinue a medication perceived as protective, may further entrench long-term use even where formal indications no longer apply^[8].

The most common reasons for inappropriate PPI use include:

- Stress ulcer prophylaxis without risk factors
- Empirical prescription for nonspecific abdominal symptoms

- Continuation of inpatient PPI therapy after discharge
- Lack of reassessment of ongoing therapy
- Misconception that PPIs are completely safe for long-term use

Healthcare professionals often prescribe PPIs prophylactically to prevent gastric irritation associated with antiplatelet drugs, corticosteroids, or NSAIDs. However, not all patients receiving these medications require acid suppression therapy, and blanket co-prescription without individual risk assessment represents a common and avoidable source of overuse. Proper risk assessment using validated criteria, such as prior ulcer history, age, and concomitant medication use, is therefore essential before initiating treatment, and should be documented clearly in the patient record to support future review [12,21].

5. ADVERSE EFFECTS ASSOCIATED WITH LONG-TERM PPI USE

Although PPIs are generally safe for short-term therapy, prolonged use has been associated with a range of adverse effects, summarized in Table 1 and discussed in greater detail below [13,14,15,16,17,18].

Table 1: Adverse Effects Associated With Long-Term PPI Use

Adverse Effect	Mechanism
Chronic kidney disease / acute interstitial nephritis	Idiosyncratic immune-mediated tubulointerstitial inflammation; cumulative nephrotoxicity with prolonged exposure ^[14]
Osteoporosis and fragility fractures	Reduced calcium absorption due to hypochlorhydria; possible inhibition of osteoclast vacuolar H ⁺ ATPase ^[15]
Clostridioides difficile infection	Loss of the gastric acid barrier permitting survival and colonization of ingested spores ^[16,17]
Community-acquired pneumonia	Upper gastrointestinal bacterial overgrowth with subsequent microaspiration ^[13,18]
Vitamin B12 deficiency	Impaired peptic cleavage of protein-bound B12 under hypochlorhydric conditions ^[13]
Hypomagnesemia	Postulated reduction in active intestinal magnesium transport (TRPM6 channel) ^[13,18]
Small intestinal bacterial overgrowth	Reduced acid barrier allowing proximal bacterial colonization ^[13]
Rebound acid hypersecretion	Gastrin-driven parietal cell hyperplasia unmasked on abrupt discontinuation ^[6]
Reduced clopidogrel efficacy	Competitive inhibition of CYP2C19-mediated clopidogrel activation (notably with omeprazole) ^[6]
Possible association with dementia	Proposed amyloid-beta or B12-mediated mechanisms; evidence inconsistent ^[27]

5.1 Renal Effects

PPI use has been associated with both acute interstitial nephritis and, with prolonged exposure, an increased risk of incident chronic kidney disease and progression to end-stage renal disease in some large cohort studies [14]. The proposed mechanism is idiosyncratic and immune-mediated in the case of acute interstitial nephritis, while the pathway underlying chronic kidney disease risk in epidemiological studies remains incompletely understood and may in part reflect unmeasured confounding, since most supporting evidence derives from observational rather than randomized data.

Clinicians should maintain a high index of suspicion for interstitial nephritis in patients on PPI therapy who develop unexplained renal impairment, and periodic renal function monitoring may be reasonable in patients on long-term therapy with additional risk factors.

5.2 Bone Health

Long-term PPI use, particularly at high doses and for durations exceeding one year, has been associated with an increased risk of osteoporosis-related fractures, most notably of the hip, wrist, and spine ^[15]. The proposed mechanism involves reduced dietary calcium absorption in the setting of hypochlorhydria, as well as a possible direct inhibitory effect on osteoclast function. Current guidance suggests that fracture risk should be considered when weighing the risks and benefits of long-term therapy in postmenopausal women and elderly patients with additional risk factors for osteoporosis, though PPI therapy alone is not considered an indication to discontinue treatment in patients with a clear ongoing clinical need.

5.3 Infections

Gastric acid provides an important barrier against ingested pathogens, and its suppression by PPIs has been consistently linked to an increased risk of *Clostridioides difficile* infection, including recurrent disease, in both community and hospital settings ^[16,17]. An association with community-acquired pneumonia has also been reported, plausibly related to bacterial overgrowth in the upper gastrointestinal tract and subsequent microaspiration, although the magnitude of this risk and its clinical significance remain debated ^[13,18]. These infection-related risks are of particular relevance in hospitalized and elderly patients, who are already at elevated baseline risk of both conditions.

5.4 Micronutrient and Metabolic Effects

Long-term acid suppression can impair the peptic digestion of protein-bound vitamin B12 in food, predisposing patients on prolonged therapy to vitamin B12 deficiency, particularly in the elderly and those with reduced dietary intake ^[13]. Hypomagnesemia has also been reported with long-term use, postulated to result from reduced active intestinal magnesium absorption, and may present with non-specific symptoms such as fatigue, muscle cramps, or cardiac arrhythmias; magnesium levels should be checked periodically in patients on long-term therapy, particularly those also taking diuretics or other magnesium-wasting drugs^[13,18].

6. DRUG INTERACTIONS AND REBOUND PHENOMENA

Omeprazole and, to a lesser extent, other PPIs metabolized through CYP2C19 can competitively inhibit the hepatic activation of clopidogrel, potentially reducing its antiplatelet efficacy; regulatory advisories have recommended avoiding this combination where possible or selecting a PPI with less CYP2C19 interaction, such as pantoprazole, in patients requiring concurrent gastroprotection^[6]. Abrupt discontinuation of long-term PPI therapy can also result in rebound acid hypersecretion, driven by gastrin-mediated parietal cell hyperplasia that develops during treatment, which may cause transient worsening of reflux symptoms and inadvertently reinforce continued, unnecessary use if misinterpreted as recurrence of the original disease ^[6]. Gradual tapering rather than abrupt cessation is therefore often recommended when discontinuing long-term therapy.

7. STRATEGIES TO IMPROVE RATIONAL USE OF PPIS

To promote appropriate use of PPIs, healthcare providers should adopt evidence-based prescribing practices such as:

- Prescribing PPIs only for approved indications
- Using the lowest effective dose
- Limiting duration of therapy to recommended periods
- Regularly reassessing the need for continued treatment
- Implementing deprescribing strategies when appropriate
- Educating clinicians and patients regarding potential risks^[19,22,28]

7.1 Deprescribing Approaches

Structured deprescribing algorithms recommend first identifying patients on long-term PPI therapy without a clear or ongoing indication, followed by either gradual dose tapering, a switch to on-demand or lowest effective dose therapy, or complete discontinuation with monitoring for symptom recurrence^[22]. Abrupt discontinuation is generally discouraged given the risk of rebound acid hypersecretion, and patients should be counselled in advance that transient symptom recurrence during tapering does not necessarily indicate ongoing need for full-dose therapy^[6,22]. Deprescribing is best undertaken opportunistically, such as at routine medication review, hospital discharge, or annual check-ups, rather than left solely to patient-initiated discussion.

7.2 Health System and Institutional Interventions

Institutional stewardship programs modelled on antimicrobial stewardship initiatives, incorporating electronic prescribing alerts, mandatory indication and stop-date documentation, and pharmacist-led review of PPI orders at admission and discharge, have been proposed as effective system-level interventions to reduce inappropriate use^[24,25]. Removing PPIs from default admission order sets and instead requiring active selection based on documented risk factors can help prevent the automatic initiation of stress ulcer prophylaxis in patients who do not meet appropriate criteria^[12].

7.3 Prescriber and Patient Education

Targeted educational interventions for prescribers, addressing appropriate indications, recommended treatment durations, and the evidence for adverse effects associated with long-term use, have been shown to reduce inappropriate prescribing in several settings^[7,23]. Patient education is equally important, since many patients perceive PPIs as entirely risk-free and may be reluctant to discontinue therapy even when no longer clinically indicated; clear communication regarding the rationale for step-down or discontinuation, along with reassurance regarding the management of any recurrent symptoms, can improve acceptance of deprescribing recommendations^[8,28].

Step-down therapy should also be encouraged, where patients with mild symptoms are managed initially with lifestyle modifications, antacids, or H2 receptor antagonists before considering long-term PPI therapy.

8. CONCLUSION

The evidence reviewed here indicates that, despite clear guidelines defining appropriate indications for PPI therapy, inappropriate and prolonged use remains common across inpatient, outpatient, and critical care settings worldwide^[1,7,9,10,11]. This gap between guideline recommendations and everyday clinical practice appears to be driven by a combination of prescriber habits, systemic prescribing defaults, and patient expectations, rather than any single identifiable cause, suggesting that effective interventions will need to be multifaceted rather than targeted at prescribers alone.

Much of the evidence linking long-term PPI use to adverse outcomes such as chronic kidney disease, fracture, and dementia is derived from observational cohort studies, which are inherently susceptible to confounding by indication and residual confounding, since patients requiring long-term acid suppression may differ systematically from those who do not in ways that independently affect these outcomes^[14,15,27]. This does not negate the clinical relevance of these associations, but it does mean that the absolute risk attributable to PPI therapy itself, as opposed to underlying patient characteristics, remains difficult to quantify precisely, and clinicians should communicate this uncertainty when counselling patients rather than presenting these risks as definitively causal.

This review has several limitations. As a narrative rather than systematic review, study selection and synthesis were not governed by a pre-registered protocol or formal quality-appraisal instrument, and publication bias favouring studies reporting significant associations cannot be excluded. Included studies were heterogeneous in design, setting, and population, limiting direct comparability of the reported prevalence estimates for inappropriate use. Restriction to English-language publications may also have excluded relevant regional data.

Future research would benefit from prospective, adequately powered studies designed specifically to quantify the independent contribution of PPI therapy to adverse outcomes, alongside pragmatic trials evaluating the real-world effectiveness of stewardship interventions such as electronic prescribing alerts and pharmacist-led deprescribing programs in reducing inappropriate use without compromising care for patients who genuinely require long-term therapy.

Proton Pump Inhibitors remain essential medications in the management of acid-related gastrointestinal disorders. However, inappropriate prescribing and prolonged use have become increasingly common in clinical practice. Irrational use of PPIs contributes to unnecessary healthcare costs, polypharmacy, adverse drug reactions, and increased risk of serious complications such as chronic kidney disease, fractures, and infections.

Evidence from recent studies indicates that a significant proportion of PPI prescriptions lack appropriate clinical indications. Therefore, clinicians must adhere strictly to evidence-based guidelines while prescribing PPIs. Regular review of therapy, proper documentation of indications, and implementation of deprescribing protocols are crucial steps toward improving rational use.

Promoting awareness among healthcare professionals regarding the risks associated with unnecessary long-term PPI therapy can help optimize patient outcomes and reduce avoidable complications. Rational prescribing practices will ensure that PPIs continue to provide maximum therapeutic benefit while minimizing potential harm. Continued research into the comparative safety of individual agents, combined with wider implementation of stewardship and deprescribing programs, will be essential to closing the persistent gap between guideline recommendations and everyday prescribing practice.

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