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# OVERPRESCRIPTION OF PROTON PUMP INHIBITORS: CAUSES, CONSEQUENCES AND STRATEGIES FOR RATIONAL USE

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**ABSTRACT**

**Background.** Proton pump inhibitors (PPIs) are effective medications widely used to manage acid-related disorders. However, their perceived safety has led to a global trend of overprescription. Therapy is often initiated during hospital stays for stress ulcer prophylaxis and continued indefinitely in primary care without a clear medical indication.
**Aim.** This narrative review aims to examine the clinical predictors and causes of PPI overuse, explore the medical consequences of long-term acid suppression, and discuss evidence-based strategies to promote rational use in clinical practice.
**Material and Methods.** The literature for this narrative review was selected from PubMed-indexed publications published between 2010 and 2026. ACG and AGA clinical guidelines, systematic reviews, and observational studies were analyzed to describe the predictors of PPI overuse, its medical consequences and evidence-based strategies for deprescribing.
**Results.** PPI overuse is primarily driven by prescribing inertia. Patient education significantly improves the success of dose reduction. While clinical decision support systems effectively reduce the initiation of inappropriate therapy, clinician acceptance of deprescribing alerts remains low compared to initiation prompts. In contrast, multidisciplinary models integrating artificial intelligence with pharmacist oversight achieve high rates of rational prescribing.
**Conclusions.** Given the massive global economic burden, PPI optimization requires a synergy of digital tools, patient education, and pharmacist-led oversight. This integrated strategy is essential for ensuring systemic sustainability and long-term medication safety.

**KEYWORDS**

Proton Pump Inhibitors, Overprescription, Deprescribing, Dysbiosis, Adverse Drug Events, Clinical Decision Support, Artificial Intelligence

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## 1. Introduction

Proton pump inhibitors (PPIs) are the most effective drugs inhibiting gastric acid secretion. They have revolutionized treatment of acid-related diseases, such as gastroesophageal reflux disease (GERD), peptic ulcer disease, and functional dyspepsia [14, 27, 34]. Due to their efficacy and perceived safety, they are among the most frequently prescribed medications worldwide. However, widespread use has led to significant overprescription, with studies estimating that many patients on chronic PPI therapy may lack a clear clinical indication [1, 18, 24].

The economic and social implications of this phenomenon are profound. PPI overprescription imposes a financial burden on healthcare systems, contributing to unnecessary medical expenditures and complicating polypharmacy management, especially in aging populations [1, 32]. Long-term PPI use is also linked to adverse clinical outcomes, including micronutrient deficiencies (magnesium, vitamin B12), increased risk of bone fractures, and higher susceptibility to infections, notably Clostridioides difficile [6, 10, 11, 12, 31, 33].

Addressing these challenges requires clinical vigilance and the implementation of “deprescribing” strategies. Recently, integrating innovative technologies has emerged as a promising way to optimize prescribing practices. Solutions like artificial intelligence (AI)-assisted decision support systems and electronic alert systems have shown potential to improve rational PPI use and enhance long-term patient safety [20, 40].

The aim of this narrative review is to evaluate the primary causes and clinical consequences of PPI overprescription, and to highlight contemporary evidence-based strategies and technological innovations for the rational use and supervised withdrawal of these agents.

## 2. Pathophysiological Background and Clinical Indications

### 2.1 Mechanism of Action and Pharmacokinetics

Proton pump inhibitors (PPIs) are benzimidazole derivatives that act as prodrugs, requiring an acidic environment for activation [2, 37]. Once ingested, they are absorbed in the small intestine and transported via the bloodstream to the gastric parietal cells. In the acidic canaliculi of these cells (pH ~1), PPIs undergo protonation and conversion into active sulfenamide forms, which form covalent disulfide bonds with cysteine residues of the α-subunit of the $H^+/K^+$-ATPase enzyme (the proton pump) [37]. This inhibition blocks the final step of gastric acid secretion, resulting in a significant and prolonged increase in gastric pH. Acid secretion resumes only after new pumps are synthesized and inserted into the canalicular membrane, a process governed by the half-life of $H^+/K^+$-ATPase in humans [37].

Beyond their primary effect on acid suppression, modern evidence in the 2025 ACG guidelines shows that PPIs also have significant non-acid-related anti-inflammatory properties. They inhibit the expression of eotaxin-3, a key chemoattractant for eosinophils, and reduce the production of Th2-mediated cytokines. This dual mechanism of acid suppression and direct anti-inflammatory action is fundamental to their efficacy as a first-line treatment for eosinophilic esophagitis (EoE) [7].

### 2.2 Evidence-Based Indications and Best Practice Guidelines (AGA/ACG)

Standardized guidelines from the ACG and AGA classify PPI therapy into short-term and long-term indications based on proven clinical benefits shown in Table 1 [14, 30].

**Table 1.** Clinical indications for short-term and long-term PPI therapy based on ACG and AGA guidelines.

| Short-term Indications (4–8 weeks) | Long-term Maintenance Indications |
|---|---|
| **Erosive Esophagitis (EE):** Standard course for healing. For mild EE (LA Grade A/B), consider dose reduction or on-demand therapy after 8 weeks [14, 30]. | **Severe Erosive Esophagitis:** Required for LA Grade C/D due to extremely high relapse rates (>90%) without therapy [30]. |
| **Peptic Ulcer Disease (PUD):** Treatment of active gastric/duodenal ulcers and H. pylori eradication protocols [34]. | **Eosinophilic Esophagitis (EoE):** Chronic anti-inflammatory treatment; 2025 guidelines emphasize indefinite use to prevent histologic relapse [7]. |
| **Functional Dyspepsia (FD):** Recommended as first-line therapy, especially for epigastric pain syndrome (EPS) [27]. | **Barrett's Esophagus:** Indefinite suppression to reduce the risk of progression to esophageal adenocarcinoma [14, 30]. |
| **Stress Ulcer Prophylaxis (SUP):** Strictly for high-risk ICU patients (e.g., mechanical ventilation >48h or coagulopathy) [22]. | **High-Risk NSAID/Aspirin Users:** Indicated for patients with a history of ulcers or those on concomitant anticoagulants/steroids [9, 30]. |
| | **Complicated GERD:** Maintenance to prevent recurrence in patients with history of peptic strictures or esophageal ulcers [30]. |
| | **Zollinger-Ellison Syndrome:** Long-term management of pathological gastric acid hypersecretion [14]. |

The AGA Clinical Practice Update stresses using the lowest effective dose for the shortest duration to avoid "prescribing inertia", where temporary prophylaxis becomes life-long treatment without re-evaluation [30].

## 3. Causes of PPI Overprescription: Drivers and Predictors

### 3.1 Hospital-Initiated Overuse: Stress Ulcer Prophylaxis and Transition of Care

Initiating PPI therapy during hospital admission is a main driver of long-term overprescription. Many unwarranted prescriptions result from inappropriate use of stress ulcer prophylaxis (SUP) in non-critically ill patients [1, 22]. The 2024 guidelines from the Society of Critical Care Medicine reserve SUP strictly for ICU patients with major risk factors, such as mechanical ventilation over 48 hours or coagulopathy [22]. Despite these clear limits, PPIs are often given to low-risk patients on general medical and surgical wards as routine gastroprotection, usually without clinical evidence [1, 38].

The most critical point in this prescribing cascade is the transition of care. Studies show that PPIs started in the hospital are rarely re-evaluated before discharge. For example, Abukhalil et al. found that 32.5% of patients admitted to internal medicine were discharged with an unnecessary ongoing PPI prescription from their stay [1]. This failure to stop treatment is not just a financial issue. Recent evidence shows it has direct clinical consequences. A 2024 study by Palmowski et al. found that failing to stop PPIs in patients who no longer met ICU criteria was linked to increased morbidity and possibly higher mortality [26]. Without thorough medication reconciliation at discharge, these temporary hospital interventions often become indefinite outpatient use because primary care providers may assume the therapy was started for a valid chronic indication [20, 23].

### 3.2 Outpatient Patterns: Polypharmacy, Aging and Prescribing Paradox

In primary care and long-term care settings, PPI overprescription is driven by a “safety illusion” and a systemic failure to align therapy with clinical risk. This creates a prescribing paradox: overuse of PPIs in low-risk patients and underuse in those who need them most.

- The Polypharmacy Trigger: Polypharmacy strongly predicts inappropriate PPI use. Clinicians often prescribe PPIs as a “default shield” for patients on complex regimens, regardless of gastrointestinal risk. Studies show the chance of receiving an unwarranted PPI rises with the number of co-prescribed medications, as providers favor “just-in-case" protection even without high-risk agents like NSAIDs [18, 33].
- The Paradox of Misalignment: The core issue is not just the volume of prescriptions but their clinical misdirection. Wabe et al. (2025) documented this paradox in nursing homes: 27.1% of PPI users exceeded recommended therapy duration (overuse), while 38.5% of high-risk patients on bleeding-risk medications did not receive gastroprotection (underuse) [36]. This shows prescribing is often driven by clinical inertia rather than individualized risk assessment.
- Low-Value Care in Older Adults: Mafi et al. (2019) found that 35.8% of PPI prescriptions in older adults were potentially low value [23]. Notably, a small group of providers (18.9%) wrote the majority (59.2%) of these prescriptions, suggesting that overprescribing is concentrated among high-volume prescribers, which could help target educational interventions [23].

### 3.3 Empiric PPI Use for Unproven Indications

The empirical use of PPIs for non-acid-mediated symptoms drives overprescription. While standard for functional dyspepsia (FD), Pasricha and Talley (2026) report their efficacy is modest, with a relative risk of no improvement at 0.86 [27]. Although ACG/CAG guidelines indicate EPS and PDS subtypes respond similarly, PPIs are often applied to all FD patients without structured evaluation of clinical benefit [18, 27]. This is sustained by the "diagnostic trial" trap, where therapy starts without a scheduled stop date and is mistakenly escalated rather than discontinued when symptoms persist [18, 24]. Many chronic users lack a confirmed GERD or ulcer diagnosis and remain on treatment for unproven indications like bloating or vague discomfort [18, 24].

### 3.4 The Prescribing Cascade and Lack of Treatment Review

Another major cause of PPI overuse is the “prescribing cascade”, occurring when a drug side effect is mistaken for a new medical condition. For PPIs, patients with minor GI distress caused by other medications - such as NSAIDs, corticosteroids, or iron supplements - are frequently initiated on acid suppression without an assessment of the primary drug’s necessity [23, 24].

Once initiated, a lack of regular treatment reviews and “clinical inertia” keep the overuse going. In many settings, repeat prescriptions are renewed automatically without doctor checks. PPIs are commonly viewed as safe, so stopping them is rarely a priority during time-constrained medication reviews [3, 20]. Because of this, even after the original triggering drug is stopped, the PPI stays on the medication list, turning a transient intervention into a lifelong, unnecessary one [6, 8].

### 3.5 Over-the-Counter Availability, Patient-Provider Dynamics and Knowledge Gaps

The widespread availability of over-the-counter (OTC) PPIs, available without prescription in the US since 2003, fosters a public perception that these medications are harmless. This leads to significant self-medication beyond the recommended 14-day OTC course without professional supervision. This normalization is reinforced by patient-provider dynamics where clinicians, often facing time constraints, yield to patient demands for "gastric protection" instead of starting complex deprescribing conversations [3, 29].

Paradoxically, the reassuring safety profile shown in recent high-certainty meta-analyses of randomized controlled trials has not confirmed most observational associations with serious adverse events - may further reduce clinician motivation to conduct regular indication reviews [25]. This happens even though the AGA emphasizes that the lack of an ongoing indication alone justifies discontinuation, regardless of the drug's safety profile [30]. Persistent knowledge gaps compound this problem bidirectionally. Targownik et al. (2022) found that about 80% of physicians would alter treatment plans based on safety concerns even in high-risk patients who clinically require PPIs. At the same time, the absence of standardized, widely implemented deprescribing protocols prevents timely withdrawal of therapy in patients without valid indications [21, 30, 38].

## 4. Consequences: Clinical Impact of Chronic Acid Suppression

### 4.1 Disruption of the Gastric Barrier: Microbiome Dysbiosis, SIBO, and Enteric Infections

Gastric acid acts as a biological filter. Chronic suppression disrupts the gastric barrier and leads to measurable shifts in the gut microbiome [33, 37]. A 2025 meta-analysis identified SIBO in 36.8% of PPI users versus 19.9% in controls. The risk rises by 4.2% for each additional month of therapy [16].

High-quality data have shifted the evidence on enteric infections. Observational studies historically linked PPIs to Clostridioides difficile (CDI) [11, 31]. However, a 2026 meta-analysis of randomized controlled trials (RCTs) involving over 30,000 participants found no significant increase in CDI risk [25]. This suggests previous associations from observational research were likely influenced by residual confounding.

The systemic impact of PPI overuse remains severe. Palmowski et al. (2024) showed that failing to stop unnecessary therapy after hospital discharge is linked to a 34% higher risk of rehospitalization, a 20% increase in 2-year mortality, and significantly higher rates of pneumonia and cardiovascular events [26]. These findings highlight that the clinical burden of chronic acid suppression manifests as increased long-term morbidity and mortality, even when specific infectious links remain unproven in clinical trials.

### 4.2 Micronutrient Malabsorption and Bone Health: Physiological and Clinical Links

Gastric acid is essential for the solubilization and absorption of several key nutrients. Chronic hypochlorhydria interferes with these biochemical processes, leading to metabolic and skeletal complications [12, 33].

- Hypomagnesemia: This severe complication occurs mainly after long-term use (typically over 1 year). PPIs disrupt intestinal magnesium transport by interfering with TRPM6/7 channel activity [10]. Clinical data show that in about 25% of cases, magnesium supplementation alone cannot correct the deficit, requiring complete PPI discontinuation for recovery [33].
- Vitamin B12 and Iron: Gastric acid and pepsin release Vitamin B12 from dietary proteins. Long-term PPI therapy significantly reduces B12 absorption, especially in older adults with limited gastric reserves [12]. Similarly, non-heme iron absorption is impaired because it requires an acidic environment to keep its soluble ferrous state [37].
- Bone Health: Chronic PPI use is linked to a modest but consistent increase in fracture risk, including a 35% higher risk of hip fractures in some observational cohorts [12]. The mechanisms include impaired absorption of insoluble calcium salts and interference with bone remodeling via osteoclast proton pumps [9, 12]. Current guidelines emphasize that, while the absolute risk is low, PPI use must be carefully reviewed in patients with high baseline osteoporosis risk [30, 38].

### 4.3 Renal Complications: From Acute Interstitial Nephritis to Chronic Kidney Disease

Long-term PPI use has been increasingly linked to adverse renal outcomes, ranging from idiosyncratic inflammatory reactions to progressive organ failure [19, 33].

- Acute Interstitial Nephritis (AIN): PPIs cause drug-induced AIN, an unpredictable immune reaction that can occur anytime during therapy. AIN is often asymptomatic or has non-specific symptoms, so it may go unrecognized and lead to irreversible tubulointerstitial fibrosis [33, 37].
- Chronic Kidney Disease (CKD): Large observational studies have linked chronic PPI therapy to a higher risk of CKD and end-stage renal disease (ESRD). Proposed mechanisms include recurring subclinical AIN episodes or chronic low-grade inflammation causing progressive renal scarring [19].
- Clinical Considerations: The AGA emphasizes considering renal health in the initial risk-benefit analysis for long-term therapy. However, current guidelines (including ACG 2022) do not recommend routine monitoring of serum creatinine or renal function for patients on PPIs without other kidney disease risk factors. Instead, clinical vigilance is advised; clinicians should monitor renal health as part of justifying continued therapy at the lowest effective dose [9, 14, 30].

### 4.4 Gastric Morphological Changes and Neoplastic Risk: Polyps and Hyperplasia

The physiologic response to chronic hypochlorhydria involves a compensatory increase in serum gastrin, a trophic hormone that stimulates the hyperplasia of parietal and enterochromaffin-like (ECL) cells [37]. Beyond the development of fundic gland polyps (FGPs), long-term acid suppression is associated with distinct endoscopic alterations, including cobblestone-like mucosa and black spots within the gastric body. These morphological changes, while characteristic of chronic PPI use, are considered benign and do not require specific intervention [34].

Regarding FGPs, studies show a nearly five-fold increase in prevalence after one year of therapy. Their malignant potential remains exceptionally low, at less than 1%. Current evidence supports a conservative management strategy, indicating that biopsy or removal of classic FGPs measuring less than 10 mm is generally unnecessary. However, their presence must prompt re-evaluation of the existing need for PPI treatment [5, 33].

The risk of gastric adenocarcinoma has been clarified by high-certainty data from a 2026 population-based study of over 1.2 million individuals. This research showed that long-term PPI use is not associated with an increased risk of gastric adenocarcinoma after adjustment for confounding factors and protopathic bias [41]. These conclusions refute earlier concerns regarding direct carcinogenesis. However, the risk of mucosal deterioration strongly depends on Helicobacter pylori status. In infected individuals, PPI therapy accelerates the progression of corpus-predominant gastric atrophy compared to those not receiving acid suppression [39].

Finally, while ECL cell hyperplasia is a common histological finding, its progression to clinical neuroendocrine tumors (NETs) is rare. Current evidence indicates that PPI-associated gastric NETs follow an indolent clinical course and have a more favorable prognosis than aggressive sporadic cases. This emphasizes that hypergastrinemia-induced changes usually follow a benign course in the absence of additional predisposing conditions, such as autoimmune atrophic gastritis [9, 10, 11].

## 5. Strategies for Rational Use: The Deprescribing Process

Deprescribing is the systematic process of identifying and stopping medications when harm outweighs benefit or when a clear clinical indication no longer exists. Given the high rates of inappropriate long-term PPI use, structured withdrawal protocols are essential to transition patients to the lowest effective dose or complete cessation [30].

Current clinical algorithms recommend a step-down approach instead of abrupt discontinuation for patients on therapy longer than six months. The main barrier to successful discontinuation is rebound acid hypersecretion (RAH), a response where gastric acid production rises significantly above pre-treatment levels after stopping acid suppression, particularly in patients treated for over 8 weeks. Symptoms such as dyspepsia and heartburn often develop within the first two weeks of cessation and are commonly mistaken by patients as a return of their underlying disease, leading to unnecessary resumption of therapy [9, 30].

The DEPRESCRIPP trial by Fournier et al. (2026) demonstrated the effectiveness of educational interventions. The study found that a dual-target approach, which provided patients with an educational brochure and physicians with a deprescribing algorithm via traditional mail, was significantly more effective than targeting physicians alone. This low-cost, low-tech method achieved meaningful clinical change. In the dual-target group, 14.9% of patients reduced their PPI dosage by at least 50%, nearly doubling the rates in the physician-only (7.7%) and usual care (7.0%) groups. The physician-only intervention had minimal impact,

with most benefit attributed to the patient-facing component. Importantly, dose reduction did not worsen clinical outcomes; the Gastroesophageal Reflux Disease Impact Scale (GIS) showed no significant differences in symptom control between groups, confirming that substantial dose reduction can be achieved without compromising patient quality of life [8]. To further mitigate RAH and improve success rates, the following strategies are recommended:

- Dose Tapering: Reducing the daily dose (e.g., from 40 mg to 20 mg) for 2–4 weeks before stopping, or moving to every-other-day dosing to allow the gastric mucosa to gradually adjust [30, 38].
- On-Demand Therapy: Transitioning patients to on-demand use, in which the medication is taken only when symptoms occur, has proven effective for maintaining symptom control in non-erosive GERD and mild esophagitis [14, 30].
- Adjuvant Support: Providing short-term rescue therapy with H2-receptor antagonists (H2RAs) or antacids during the first 1–2 weeks of PPI withdrawal to manage transient breakthrough symptoms [30].

The decision to deprescribe must be shared between the clinician and the patient, focusing on those with healed mild esophagitis, uncomplicated peptic ulcers, or those who were started on PPIs during hospitalization without a clear outpatient indication. Modern interventions, including those led by clinical pharmacists, are increasingly utilizing automated tools to identify these candidates, ensuring that therapy remains aligned with current safety guidelines [9, 30, 40].

## 6. Innovative Technologies as Strategies for Optimization

### 6.1 Electronic Clinical Decision Support Systems (CDSS)

Electronic Clinical Decision Support Systems (CDSS) act as key technological links between evidence-based guidelines and real-time clinical decisions. When integrated with Electronic Health Records (EHR), these systems provide automated prompts that reduce prescribing inertia and inappropriate proton pump inhibitor (PPI) initiation at the point of care [20, 25, 42]. Luo et al. (2025) demonstrated the efficacy of such systems, showing that a contextual electronic alert system integrated with physician orders significantly reduced overall PPI prescribing and markedly decreased high-dose therapy [20]. The effectiveness of these interventions can be further improved by incorporating a pharmacist-led evaluation phase. For example, Flückiger et al. (2024) found that a CDSS algorithm combined with pharmacist review reduced missing gastroprotection by 63.4% and inappropriate PPI prescriptions by 16.2% at hospital discharge [42].

A primary advantage of CDSS is promoting diagnostic accountability. Modern systems use hard-stop or soft-stop mechanisms that require clinicians to select a validated indication from a predefined list before completing an electronic PPI prescription. However, the effectiveness of these alerts varies by clinical intent. Evidence shows physicians are more likely to accept alerts for initiating necessary therapy (73% acceptance) than for discontinuing inappropriate prescriptions (34% acceptance) [42]. This prescribing inertia highlights the need for CDSS to deliver highly specific, patient-tailored recommendations to overcome clinical resistance [20, 42].

CDSS also play a critical role in maintaining continuity of care at hospital discharge. Automated alerts identify patients started on acid suppression during hospitalization without a long-term indication, prompting the care team to implement a tapering plan during discharge reconciliation. By continuously monitoring all adult hospitalizations and flagging cases where therapy began without a documented outpatient need, these systems provide a strong mechanism for medication safety. They ensure both underuse and overuse are addressed before the patient's transition to outpatient care [30, 42].

### 6.2 AI-Assisted Quality Circles and Pharmacist Interventions

The integration of clinical pharmacists into multidisciplinary teams is fundamental to rational proton pump inhibitor (PPI) prescribing, especially when supported by structured quality improvement frameworks [30, 40]. In the study by Zhang et al. (2025), Artificial Intelligence (AI) was applied within the Quality Control Circle (QCC) framework as an analytical tool for root cause analysis [40]. AI supported the team during the brainstorming phase to identify underlying causes of irrational PPI use, with particular attention to the overutilization of parenteral therapy, which is often continued in hospitalized patients despite the clinical feasibility and equivalent efficacy of oral alternatives [30, 40].

Within this framework, AI serves as an analytical aid that enhances the planning stages of interventions rather than acting as a passive screening system [40]. By improving the identification of systematic prescribing errors and their underlying causes, AI enabled clinical pharmacists to implement more targeted strategies [40]. The adoption of these AI-assisted QCCs increased the rational PPI application rate from 66.51% to 93.43%, indicating that the combination of clinical expertise and AI-driven analytical planning can significantly optimize medication safety [40].

## 7. Discussion

This review identifies a significant paradox: although proton pump inhibitors (PPIs) are indispensable for managing acid-related disorders, their widespread overprescription has resulted in a global public health concern. The shift from acute, indication-based therapy to unintended chronic use is primarily driven by prescribing inertia, patient expectations, and systemic deficiencies in discharge reconciliation [9, 20, 42].

A primary obstacle to rational use is rebound acid hypersecretion (RAH), which often leads to therapy resumption as patients mistake withdrawal symptoms for disease recurrence [9, 30]. The DEPRESCRIPP trial (Fournier et al., 2026) demonstrates that clinical algorithms alone are insufficient; they must be paired with patient education [8]. By using a simple educational brochure, the trial nearly doubled the dose-reduction success rate (14.9% vs. 7.0%) without compromising quality of life, as evidenced by stable Gastroesophageal Reflux Disease Impact Scale (GIS) scores [8].

CDSS and AI Digital tools, such as clinical decision support systems (CDSS) and artificial intelligence (AI), have become essential safeguards; however, their effectiveness relies on clinician acceptance. Luo et al. (2025) confirm that real-time CDSS alerts reduce unnecessary therapy initiation [20]. In contrast, Flückiger et al. (2024) highlight a critical gap: physicians are substantially more likely to accept alerts for initiating therapy (73%) than for discontinuing it (34%) [42].

To address this resistance, automated systems should be integrated with multidisciplinary expertise. The AI-assisted Quality Control Circle (QCC) model (Zhang et al., 2025) demonstrates that AI's primary value is its analytical ability to identify root causes of overuse, rather than serving solely as a passive alert system [40]. This pharmacist-led, AI-supported framework achieved a rational PPI application rate exceeding 93%, indicating that technology is most effective when it augments human clinical judgment [40].

The economic imperative for optimization is underscored by staggering global costs. According to Fournier et al. (2026), PPI reimbursement reached $12 billion in the United States (2015) and £87 million in England (2018) [8]. These figures reflect not only direct drug expenditures but also the indirect costs of managing long-term complications, such as renal impairment and infections. Pharmacist-led interventions, supported by AI and CDSS, offer a sustainable pathway to mitigate these costs by preventing hospital-initiated prophylaxis from transitioning into lifelong outpatient use [20, 40, 42].

Future Directions Future strategies should prioritize reducing alert fatigue and incorporating behavioral nudges to address physician resistance to deprescribing. Additional longitudinal research is necessary to assess the long-term effects of pharmacist-led AI interventions in various clinical environments.

## 8. Conclusions

The widespread overprescription of proton pump inhibitors constitutes a significant systemic challenge, driven by prescribing inertia, improper hospital-initiated prophylaxis, and inadequate medication reconciliation at discharge. With reimbursement costs reaching $12 billion in the United States and £87 million in England, the economic burden underscores the urgent need for evidence-based optimization strategies [8].

Importantly, this review highlights that the risk profile of PPIs has been substantially refined by recent high-certainty data. Randomized controlled trial evidence has failed to confirm previously reported observational associations between PPIs and Clostridioides difficile infection, while large population-based studies have effectively refuted a direct link between long-term PPI use and gastric adenocarcinoma. However, the risk of accelerated gastric mucosal deterioration in Helicobacter pylori-positive patients remains well-established, reinforcing that H. pylori testing and eradication should be considered a standard component of care before initiating long-term acid suppression therapy [30, 39].

Effective de-implementation of chronic PPI therapy requires a multifaceted approach grounded in established guidelines. As demonstrated in the DEPRESCRIPP trial, clinical algorithms achieve significantly greater success when combined with direct patient education, addressing key barriers such as fear of symptom recurrence and misinterpretation of rebound acid hypersecretion [8]. Technological interventions, including CDSS and AI-assisted quality improvement frameworks, serve as essential force multipliers; however, their effectiveness in promoting deprescribing remains limited by clinician resistance, necessitating context-aware, high-specificity alert design [20, 42]. Ultimately, the most sustainable model for rational PPI use integrates pharmacist-led clinical oversight with technology-driven surveillance, ensuring that every prescription remains aligned with a documented, evidence-based indication [40, 42].

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