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OPTIMIZING LONG-TERM PROTON PUMP INHIBITOR THERAPY THROUGH DEPRESCRIBING: A CRITICAL REVIEW OF CURRENT EVIDENCE, CLINICAL OUTCOMES, AND FUTURE PERSPECTIVES

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ABSTRACT

Background: Proton pump inhibitors (PPIs) are among the most frequently prescribed medications worldwide for the management of acid-related disorders. However, prolonged use beyond evidence-based indications has become increasingly common, exposing patients to avoidable adverse effects and contributing to unnecessary healthcare expenditure. **Objective:** This review aims to critically evaluate current evidence regarding PPI deprescribing and de-escalation strategies, examine their clinical outcomes and safety profiles, and explore emerging stewardship approaches for optimizing long-term PPI therapy. **Methods:** Relevant original studies, randomized controlled trials, observational studies, pharmacovigilance analyses, and stewardship interventions published between 2010 and 2026 were reviewed using literature retrieved from PubMed, PubMed Central, and related databases. **Results:** Current evidence demonstrates that structured, patient-centered deprescribing interventions, including dose tapering, abrupt discontinuation, pharmacist-led stewardship programs, and multidisciplinary care models, can successfully reduce inappropriate long-term PPI use in a substantial proportion of patients. Although rebound acid hypersecretion remains a challenge, appropriate patient education, follow-up, and rescue therapy strategies improve deprescribing success. Emerging evidence also supports the cost-effectiveness and clinical benefits of structured PPI stewardship programs. **Conclusion:** PPI deprescribing represents an effective strategy for optimizing medication use while minimizing unnecessary exposure to long-term adverse effects. Future efforts should focus on individualized deprescribing approaches, clinical decision support systems, multidisciplinary stewardship programs, and implementation strategies that promote sustainable medication optimization.

KEYWORDS: Proton pump inhibitors; Deprescribing; De-escalation; PPI stewardship; Long-term PPI use; Clinical outcomes; Adverse drug reactions; Medication optimization.

1. INTRODUCTION

Proton pump inhibitors (PPIs) are among the most widely prescribed medications worldwide and are considered the cornerstone of therapy for acid-related disorders, including gastroesophageal reflux disease, peptic ulcer disease, Helicobacter pylori eradication, and prevention of nonsteroidal anti-inflammatory drug-induced gastrointestinal complications. Their efficacy and favourable short-term safety profile have contributed to their widespread use; however, prolonged therapy beyond evidence-based indications has become increasingly common.

Several studies have demonstrated that a substantial proportion of patients receiving long-term PPI therapy lack an appropriate indication for continued treatment. Factors contributing to inappropriate use include continuation of therapy initiated during hospitalization, inadequate reassessment of treatment necessity, patient preference, and the perception that PPIs are relatively harmless medications. Growing evidence has associated prolonged PPI exposure with adverse outcomes, including renal disorders, infections, fractures, and micronutrient deficiencies, prompting recommendations for regular reassessment and deprescribing when appropriate.

Despite increasing awareness of PPI overuse, implementation of deprescribing strategies remains challenging due to concerns regarding symptom recurrence, rebound acid hypersecretion, patient expectations, and variability in clinical practice. Recent studies have evaluated various deprescribing approaches, including tapering strategies, pharmacist-led interventions, stewardship programs, and multidisciplinary care models.

Although several reviews have addressed PPI deprescribing, limited attention has been given to integrating recent evidence on clinical outcomes, stewardship interventions, economic implications, and future approaches to medication optimization. Therefore, this review aims to synthesize current evidence regarding PPI de-escalation strategies, adverse effects associated with long-term use, multidisciplinary interventions, and emerging approaches for optimizing PPI therapy in clinical practice. Unlike traditional narrative reviews, this critical review evaluates the quality, strengths, limitations, and clinical applicability of current evidence regarding proton pump inhibitor deprescribing. Particular emphasis is placed on methodological limitations, inconsistencies in available evidence, implementation challenges, and opportunities for future research and clinical practice improvement.

Research Gap and Rationale for the Present Review

Although several reviews have previously examined proton pump inhibitor deprescribing, limited attention has been given to integrating recent evidence regarding clinical outcomes, multidisciplinary stewardship interventions, economic implications, and emerging approaches to medication optimization. Furthermore, rapidly evolving evidence published over the past decade warrants an updated synthesis to guide clinical practice.

Therefore, this review aims to provide a comprehensive overview of current evidence regarding proton pump inhibitor deprescribing strategies, adverse effects associated with long-term therapy, multidisciplinary interventions, economic outcomes, and future directions for optimizing PPI use in clinical practice.

2. METHODS

Review Design

This study was conducted as a critical review aimed at evaluating and synthesizing current evidence regarding proton pump inhibitor (PPI) deprescribing strategies, clinical outcomes, stewardship interventions, economic implications, and

future directions. In addition to summarizing available evidence, this review critically appraises the strengths, limitations, and applicability of current research findings to clinical practice.

Literature Search Strategy

A comprehensive literature search was conducted using PubMed, PubMed Central (PMC), Google Scholar, and other relevant electronic databases to identify studies published between January 2010 and June 2026 related to proton pump inhibitor deprescribing and de-escalation.

Randomized controlled trials, observational studies, pharmacovigilance analyses, implementation studies, and economic evaluations were included. Relevant information regarding study design, interventions, clinical outcomes, adverse effects, and stewardship strategies was extracted and narratively synthesized.

Eligibility Criteria

The review included randomized controlled trials, observational studies, pharmacovigilance studies, implementation studies, economic evaluations, systematic reviews, and clinical practice guidelines relevant to PPI deprescribing.

Data Extraction and Synthesis

Relevant information regarding study design, patient population, interventions, outcomes, adverse effects, and stewardship strategies was extracted and narratively synthesized to provide a comprehensive overview of current evidence.

3. Scope and drivers of PPI overuse

Quantifying inappropriate PPI use has been a recurring focus of observational research. A large Dutch primary care cohort encompassing nearly 150,000 patients found that only 44% of new PPI prescriptions had a clearly valid indication at initiation, with older age and concurrent use of nonselective NSAIDs, P2Y12 inhibitors, COX-2 inhibitors, and low-dose aspirin most strongly predicting inappropriate initiation; even where an initial indication existed, continuation beyond the clinically warranted duration was documented in roughly a third of short-term users.[1] A global synthesis of prescribing trends similarly concluded that PPI utilization has risen steadily across health systems, with overuse identified as a near-universal pattern rather than an isolated phenomenon confined to particular regions or care settings.[2]

Hospital-based studies reinforce this picture from a different angle. Retrospective cohort data on patients managed endoscopically for peptic ulcer disease found that a substantial share continued PPI therapy well beyond the eight-week duration recommended by regulatory labelling, with healthcare utilization patterns – rather than clinical severity alone – helping explain prolonged prescribing [3]. Within gastroenterology practices, deprescription rates among patients treated for upper gastrointestinal bleeding rose meaningfully after the dissemination of formal deprescribing guidelines, yet remained well below the proportion of patients for whom discontinuation would have been clinically appropriate.[4]

Qualitative research adds insight into why these patterns persist. General practitioners interviewed about PPI deprescribing described a mix of clinical caution, time constraints during consultations, uncertainty about how patients will respond to dose reduction, and a lack of clear local protocols as recurring barriers, even when prescribers personally endorsed the principle of stewardship [5]. Surveys of older PPI users and their providers have similarly found that patient apprehension about symptom recurrence, combined with provider uncertainty regarding current guidelines,

frequently stalls deprescribing conversations before they begin [6]. Collectively, these findings indicate that PPI overuse is sustained less by disagreement over the underlying evidence than by structural and behavioural barriers within everyday clinical workflows – precisely the barriers that targeted de-escalation interventions are designed to address.

4. Critical Evaluation of De-escalation and Discontinuation Strategies

A central practical question in PPI deprescribing is whether gradual dose tapering offers a meaningful advantage over abrupt discontinuation. Rebound acid hypersecretion – a transient increase in gastric acid output and associated dyspeptic symptoms following cessation – has long been cited as the principal barrier to successful withdrawal. A placebo-controlled trial in healthy, Helicobacter pylori-negative volunteers demonstrated that even a four-week course of pantoprazole could induce measurable dyspeptic symptoms after discontinuation in previously asymptomatic participants, with symptom severity correlating with elevated gastrin and chromogranin-A levels, providing physiological grounding for clinicians' caution around stopping therapy abruptly.[7]

Building on this mechanistic understanding, a randomized open-label trial directly compared abrupt discontinuation against a tapering protocol in patients with GERD followed for twelve months. Kaplan-Meier survival analysis found no statistically significant difference between the two strategies in the proportion of patients who remained off PPIs at twelve months, though the tapering group reported significantly fewer symptoms at multiple intervals between fourteen and thirty weeks after discontinuation, suggesting that tapering may improve the subjective withdrawal experience even where it does not clearly improve long-term discontinuation success.[8] A separate prospective study of PPI deprescription in hospitalized patients without a valid ongoing indication likewise compared gradual versus abrupt withdrawal strategies and assessed the proportion of patients who required reintroduction of therapy due to rebound digestive symptoms, contributing further pragmatic, real-world evidence to this comparison.[9]

Beyond pharmacologic tapering, adjunctive strategies have been tested to ease the withdrawal period. A randomized trial examining structured alginate use during the mandatory PPI washout period preceding oesophageal pH and impedance testing found that regular alginate dosing helped maintain control of reflux symptoms and improved patient compliance with the washout protocol, offering a practical tool for managing symptom burden during a defined high-risk discontinuation window [11]. Similarly, a placebo-controlled primary care trial assessing discontinuation of long-term PPI therapy found that short-term reintroduction of esomeprazole was more effective than placebo specifically among patients who experienced symptom relapse after stopping, underscoring that a substantial minority of patients will need a structured “rescue” pathway rather than a single attempt at permanent cessation.[10]

Rebound acid hypersecretion is a recognized phenomenon following discontinuation of proton pump inhibitors and may result in transient upper gastrointestinal symptoms. This effect can lead patients and clinicians to misinterpret temporary symptom recurrence as relapse of the underlying disease, thereby contributing to unnecessary reinitiation of therapy. Patient education regarding the expected course of withdrawal and appropriate follow-up are therefore essential components of successful deprescribing strategies.[7,8] Taken together, this body of evidence suggests that while tapering does not guarantee higher rates of permanent discontinuation compared with abrupt cessation, it appears to reduce the symptomatic burden experienced by patients during withdrawal, and pairing either strategy with patient education, anticipatory guidance about rebound symptoms, and a clear plan for symptom rescue improves the overall feasibility of de-escalation.

Table 2: Comparison of Proton Pump Inhibitor Deprescribing Strategies.

Strategy	Description	Advantages	Limitations	Clinical Outcome
Abrupt discontinuation	Immediate cessation of PPI therapy	Simple and rapid	Higher risk of rebound symptoms	Moderate success
Dose tapering	Gradual reduction of dose over weeks	Reduced rebound symptoms	Longer duration	Good success
Alternate-day dosing	Administration on alternate days	Better patient tolerance	Variable efficacy	Moderate to good success
Step-down therapy	Transition to lower potency acid suppression	Improved symptom control	Requires monitoring	Good success
Pharmacist-led deprescribing	Structured multidisciplinary intervention	High acceptance and adherence	Resource intensive	High success
Rescue therapy approach	Temporary reintroduction during relapse	Improves patient confidence	Possible re-initiation	Improved long-term adherence

The available evidence suggests that no single deprescribing strategy is universally superior. Successful PPI deprescribing depends on individualized patient assessment, clinical indication, patient preference, and the availability of structured follow-up and multidisciplinary support.

5. Multidisciplinary stewardship interventions across care settings

Hospital-based pharmacist-led stewardship:

Inpatient settings have proven a fertile environment for structured PPI stewardship, largely because hospitalization frequently both initiates and perpetuates inappropriate use. A retrospective cohort evaluation of a pharmacist-led inpatient PPI stewardship program found that the overwhelming majority of patients – nearly 96% – tolerated inpatient PPI discontinuation when the stewardship team identified an absence of valid indication, with the large majority requiring no rescue acid-suppressive therapy during their hospital stay; however, success at three months post-discharge was considerably lower, with just over half of patients remaining off PPIs and roughly four in five tolerating dose de-escalation rather than full discontinuation, highlighting a persistent gap between inpatient and sustained outpatient success.[12]

A complementary feasibility study leveraged an existing antimicrobial stewardship infrastructure to support a pharmacy-led, non-guideline-concordant PPI de-implementation initiative, reasoning that the shared goal of reducing Clostridioides difficile infection risk created natural synergy between antimicrobial and PPI stewardship programs; the intervention required iterative stakeholder engagement with inpatient pharmacist and physician workgroups to refine process measures before full implementation.[13] In French hospitals, an observational study characterizing pharmacist interventions specifically targeting PPI prescriptions found that pharmacist recommendations addressing dosing, duplicate therapy, and lack of indication were accepted by prescribing physicians at a clinically meaningful rate, reinforcing the value of embedding pharmacists within multidisciplinary ward teams rather than relying on isolated educational campaigns.[14]

At a health-system level, an interrupted time-series analysis from a tertiary hospital in northwestern China evaluated the impact of national PPI utilization guidelines and a key-monitoring-drug policy implemented through clinical pharmacist-led stewardship, finding a measurable reduction in defined daily dose per hundred bed-days following the introduction of national guidelines, although the effect did not translate into a sustained downward time trend across the full eight-year observation period, suggesting that policy-level interventions require ongoing reinforcement rather than

a single implementation event to achieve durable change [15]. Despite encouraging outcomes from pharmacist-led stewardship interventions, many available studies are single-center investigations with limited external validity. Furthermore, differences in healthcare infrastructure and resource availability may limit the generalizability of these findings across healthcare systems.

Primary care and ambulatory interventions

In primary care settings, structured deprescribing algorithms, patient education, and multidisciplinary interventions have shown promising results in reducing inappropriate long-term PPI use.[16,17] Large pragmatic and cluster-randomized studies further support the effectiveness of combined patient- and provider-focused interventions, educational programs, and clinical decision support systems in promoting evidence-based deprescribing practices.[18–22]

Long-term care and geriatric populations

Older adults represent a high-risk population for inappropriate long-term PPI use. Studies conducted in nursing homes, ambulatory geriatric clinics, and multimorbidity cohorts have demonstrated that structured deprescribing protocols and interdisciplinary care approaches can safely reduce PPI use while improving medication appropriateness.[23–26]

However, maintaining successful deprescribing during transitions of care remains a significant challenge.

6. Adverse Drug Reactions Associated with Long-Term PPI Use

The rationale for PPI de-escalation is supported by accumulating evidence linking prolonged PPI use to several adverse outcomes, although the strength of evidence varies across different conditions. Pharmacovigilance studies have identified renal and gastrointestinal disorders, hypomagnesemia, hypocalcaemia, and anaemia as frequently reported adverse events, with elderly patients disproportionately affected.[27,28]

Renal complications have received particular attention. However, findings from the prospective ASSESS-AKI cohort suggest that PPI use may not independently increase the risk of post-hospitalization acute kidney injury after adjustment for confounding factors, highlighting the complexity of interpreting observational associations.[29]

Long-term PPI therapy has also been associated with fractures, Clostridioides difficile infection, community-acquired pneumonia, micronutrient deficiencies, hypergastrinemia, and gastrointestinal mucosal changes.[30] Nevertheless, much of the available evidence remains observational, and causality has not been definitively established. Therefore, periodic reassessment of PPI therapy and a risk-stratified approach to deprescribing are recommended, particularly for patients without a valid long-term indication.[30]

Most evidence linking long-term PPI therapy to adverse outcomes is derived from observational studies and pharmacovigilance analyses, which are susceptible to residual confounding and reporting bias. Therefore, caution should be exercised when interpreting causal relationships between prolonged PPI exposure and adverse clinical outcomes.

7. Critical Appraisal of Current Evidence

The evidence supporting proton pump inhibitor (PPI) deprescribing has expanded substantially over the past decade and includes randomized controlled trials, prospective observational studies, pharmacovigilance analyses,

implementation studies, and economic evaluations conducted across multiple healthcare settings. This diverse body of evidence strengthens the overall understanding of deprescribing strategies and their clinical applicability.

Several strengths of the current evidence base deserve recognition. First, numerous studies have demonstrated the feasibility and safety of structured PPI deprescribing interventions in hospital, primary care, and long-term care settings. Second, pharmacist-led and multidisciplinary stewardship approaches have consistently shown favourable outcomes in reducing inappropriate long-term PPI use. Third, emerging economic evaluations suggest that deprescribing interventions may provide substantial cost savings while maintaining patient safety and quality of care.

Several methodological limitations deserve consideration. Many studies have small sample sizes, short follow-up periods, and heterogeneous outcome measures. Additionally, there is a paucity of high-quality randomized controlled trials evaluating long-term deprescribing outcomes. Publication bias and limited evidence from low- and middle-income countries further restrict the generalizability of current findings.

Despite these strengths, several limitations remain. Many studies have relatively small sample sizes and short follow-up periods, limiting the assessment of long-term sustainability. Considerable heterogeneity exists in patient populations, deprescribing protocols, and outcome measures, making direct comparisons challenging. Furthermore, evidence from low- and middle-income countries remains limited, and the long-term impact of deprescribing on patient-centered outcomes requires further investigation. Future large-scale, multi-center studies with standardized outcome measures are necessary to strengthen the evidence base and support broader implementation of PPI stewardship initiatives.

Table 3: Reported Adverse Effects Associated with Long-Term Proton Pump Inhibitor Use.

Organ System	Adverse Effect	Evidence Strength	Proposed Mechanism
Renal	Acute kidney injury, chronic kidney disease	Moderate	Interstitial nephritis, altered renal function
Skeletal	Osteoporosis, fractures	Moderate	Reduced calcium absorption
Gastrointestinal	Clostridioides difficile infection	Strong	Altered gastric pH and microbiome
Nutritional	Vitamin B12 deficiency	Moderate	Reduced gastric acid secretion
Electrolytes	Hypomagnesemia	Strong	Impaired magnesium absorption
Infectious	Community-acquired pneumonia	Weak to moderate	Reduced gastric barrier function
Hematologic	Iron deficiency anaemia	Moderate	Reduced iron absorption
Gastrointestinal mucosa	Polyps, intestinal metaplasia	Moderate	Hypergastrinemia and mucosal changes

Although many adverse effects associated with long-term PPI use have been identified through observational studies and pharmacovigilance analyses, the strength of causal evidence varies considerably among different outcomes. Therefore, clinical decisions regarding deprescribing should be individualized based on patient-specific risk-benefit assessment and the presence of a valid therapeutic indication.

8. Economic and health-system outcomes of deprescribing

Beyond individual clinical risk, PPI overuse imposes a measurable economic burden that has motivated health-system-level interest in deprescribing as a cost-containment strategy alongside its clinical rationale. A decision-analytic cost-effectiveness analysis modelling a structured PPI deprescribing service against usual care in a hypothetical cohort of older PPI users within Hong Kong's public healthcare system found that the deprescribing pathway was associated with

favourable cost-effectiveness, driven by reduced medication expenditure and avoidance of downstream adverse-event-related costs, even after accounting for the modest additional costs of structured monitoring and follow-up.[32]

Complementary protocol-stage work for a Portuguese pragmatic non-randomized controlled trial – the C-SENIoR study – has been designed explicitly to evaluate both clinical effectiveness and cost-effectiveness of a collaborative deprescribing intervention involving community pharmacists and general practitioners working in tandem to support community-dwelling older adults, reflecting growing recognition that economic evaluation should be built into deprescribing trial design from the outset rather than estimated retrospectively.[33] At the institutional level, an evaluation of clinical pharmacist-driven taper recommendations delivered electronically to primary care providers ahead of schedule appointments found measurable reductions in average prescription volume following the intervention, translating clinical de-escalation directly into reduced pharmaceutical expenditure at the population level within that practice.[34]

Overall, available economic evidence suggests that structured deprescribing interventions may improve medication appropriateness while reducing unnecessary healthcare expenditure. These findings support the incorporation of stewardship programs into routine clinical practice, although additional prospective cost-effectiveness studies are required to confirm long-term economic benefits across different healthcare systems.

9. Barriers, facilitators, and a proposed framework for ppi optimization

Synthesizing the intervention literature alongside qualitative research on prescriber and patient perspectives reveals a consistent set of facilitators associated with successful de-escalation. Structured algorithms that clearly define eligibility for deprescribing reduce reliance on individual clinical judgment under time pressure; multidisciplinary involvement, particularly the integration of pharmacists into the deprescribing workflow, appears repeatedly across both hospital and ambulatory settings as a feature of higher-performing interventions; patient education addressing the expected timeline and management of rebound symptoms reduces premature reinitiation; and structured follow-up scheduled within the high-risk withdrawal window allows timely intervention with rescue therapy when needed rather than abandonment of the deprescribing attempt altogether.

Conversely, recurring barriers include prescriber uncertainty about current guidelines, fragmented communication across care transitions – particularly from hospital discharge into primary care follow-up – and patient anxiety rooted in prior negative experiences with symptom recurrence. Addressing these barriers requires interventions operating simultaneously at the system, provider, and patient level rather than relying on any single lever.

Drawing on this synthesis, we propose a practical framework for PPI optimization built around four sequential components: first, systematic indication review at defined clinical touchpoints, including hospital discharge and routine medication reconciliation, using a structured eligibility algorithm rather than ad hoc judgment; second, shared decision-making with the patient that explicitly anticipates rebound symptoms and establishes a mutually agreed tapering or discontinuation plan; third, active involvement of pharmacists as care navigators throughout the de-escalation process, particularly during care transitions where deprescribing gains are most often lost; and fourth, scheduled follow-up within the first two to four weeks after dose reduction or cessation, with a predefined rescue pathway should symptoms recur. This framework reflects the convergent lessons of the trials and stewardship programs reviewed above and offers a template adaptable across hospital, primary care, and long-term care settings.

10. Future directions and emerging approaches in ppi deprescribing

Future PPI deprescribing strategies are likely to incorporate personalized, technology-supported approaches to medication optimization. Clinical decision support systems, electronic prescribing alerts, and pharmacist-led stewardship programs may improve the identification of patients receiving inappropriate long-term PPI therapy.

Artificial intelligence and machine learning tools also have the potential to support individualized deprescribing decisions by predicting treatment success and adverse outcomes. Future research should prioritize large multi-center studies, standardized outcome measures, patient-centered outcomes, and cost-effectiveness analyses to strengthen the evidence base for PPI deprescribing. Future research should prioritize adequately powered multicenter randomized controlled trials, standardized outcome measures, patient-reported outcomes, and implementation science approaches to improve the quality and applicability of evidence supporting PPI deprescribing.

11. Limitations of the Review

This critical review has several limitations. Formal systematic review methodology and quantitative meta-analysis were not performed. Although efforts were made to critically evaluate the available literature, interpretation remains subject to the inherent limitations of narrative synthesis. Furthermore, heterogeneity among study designs and patient populations limited direct comparisons between studies.

12. CONCLUSION

Proton pump inhibitors remain essential therapies for appropriately selected patients; however, their prolonged use beyond evidence-based indications continues to represent a significant clinical challenge. Current evidence demonstrates that structured deprescribing interventions, including tapering strategies, pharmacist-led stewardship programs, and multidisciplinary approaches, can effectively reduce inappropriate long-term PPI use while maintaining patient safety.

Although concerns regarding rebound symptoms and adverse outcomes persist, patient education, individualized treatment plans, and structured follow-up can improve the success of deprescribing interventions. Emerging evidence also supports the clinical and economic benefits of PPI stewardship programs. Future efforts should focus on the implementation of evidence-based, patient-centered deprescribing strategies and the development of standardized approaches to optimize long-term PPI therapy across diverse healthcare settings.

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Conflicts of Interest

The authors declare no conflict of interest.

Author Contributions

Al Febina Nivas conceptualized the review topic, conducted the literature search, analysed and synthesized the evidence, and prepared the original manuscript draft. Binai Sankar provided supervision, guidance, and critical revision of the manuscript throughout the study. Fathima Shafna Karunakarath contributed to manuscript review and revision.

Nithin Kinattukaraparambil participated in manuscript editing and critical evaluation of the content. All authors reviewed, approved, and agreed to the final version of the manuscript for publication.

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