

Increasingly Recognized Long-term Side Effects of Proton Pump Inhibitors



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ABSTRACT

Proton pump inhibitors (PPIs) are the most commonly prescribed medicines to treat gastroesophageal reflux disease (GERD) and peptic ulcers. However, prolonged use of PPIs has been connected to many complications. These include pneumonia and *Clostridioides difficile* infection (CDI), which may result from impaired nutrient absorption due to hypochlorhydria; cognitive decline associated with reduced amyloid beta peptide clearance and decreased acetylcholine production; osteoporosis caused by a calcium absorption defect and transient receptor potential melastatin 6/7 (TRPM6/7)-linked dysregulation of bone remodeling; chronic kidney disease (CKD) driven by acute interstitial nephritis and vascular calcifications resulting from hypomagnesemia; and an increased risk of metabolic syndrome with type 2 diabetes mellitus. Given these potential adverse effects, health care providers must use PPIs carefully, ensuring that treatment is necessary at the start and continually reevaluated during long-term use.

Keywords: Adverse events, Gut microbiota, Hypergastrinemia, Proton pump inhibitors.

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INTRODUCTION

Proton pump inhibitors (PPIs) have become a mainstay in modern medical treatment, widely endorsed by clinicians due to their proven efficacy and strong safety profile in managing gastroesophageal reflux disease (GERD). In addition, PPIs play a significant role in healing peptic ulcer-related disease and minimizing the risk of gastropathy related to nonsteroidal anti-inflammatory drugs (NSAIDs), reinforcing their position as a go-to therapeutic option.¹ These agents act on parietal cells and block the H⁺/K⁺-ATPase enzyme. However, these very properties have also led to the widespread overuse and inappropriate prescribing of PPIs. Many physicians continue recommending them for extended durations, while a substantial number of patients use them without medical oversight, often purchasing them over the counter. Additionally, aggressive marketing by pharmaceutical companies has contributed to this trend. Adverse outcomes such as lupus erythematosus, acute interstitial nephritis (AIN), hypomagnesemia, bone fractures, and vitamin deficiency—several of which have been highlighted in Food and Drug Administration (FDA) warnings—are increasingly associated with long-term use.² Numerous international studies have reported that PPIs are frequently used in both inpatient and outpatient settings. The two major concerns tied to prolonged PPI use are the elevated cost of therapy and the heightened risk of side effects.

EVIDENCE-BASED DEPLOYMENT OF PROTON PUMP INHIBITOR: NAVIGATING THE PITFALLS OF OVERUTILIZATION

Proton pump inhibitors have provided significant therapeutic benefits, greatly improving the lives of patients with refractory GERD and the risk of iatrogenic upper gastrointestinal issues. Short-term use of PPIs has shown effectiveness in managing various gastrointestinal disorders, including peptic ulcer disease. However, excessive prescribing of PPIs remains common in both primary and secondary care settings. While their use is justified for patients with persistent acid-related symptoms or a high risk of developing such conditions, irrational prescribing practices have become widespread. This inappropriate use not only raises the risk of adverse drug reactions but also leads to unnecessary health care expenses.

A large part of this excessive use originates in primary health care centers, where patients are often kept on long-term PPI therapy without reevaluation.³ A study conducted at different centers revealed that PPI use was highest in intensive care units (ICUs), where 95% of patients received PPIs, with pantoprazole being the most commonly prescribed, accounting for nearly 90% of cases. Additionally, about one-third of PPI administrations were intravenous, mainly within medical wards. Almost 90% of admitted patients were prescribed a PPI.⁴ Self-

medication and unmonitored use of PPIs are also major concerns, frequently leading to drug interactions and side effects. A prospective survey from a rural teaching hospital suggests that almost 50% of patients used PPIs without clear clinical indications. Among them, 64% either received prescriptions from unqualified sources or purchased the medications without medical approval.

Patient-specific factors, such as age, underlying health conditions, genetic traits, and concurrent medications, play a crucial role in determining the likelihood and severity of side effects from PPI use. Including patient perspectives in future research can help better understand the risks and improve therapeutic outcomes through patient-centered care.⁵ Another concern is rebound acid hypersecretion that may occur after stopping PPIs following several weeks of use, often resulting in resumed therapy and potential long-term dependence.⁶ To improve appropriate PPI use, health care providers should conduct personalized risk assessments to identify individuals most vulnerable to adverse outcomes. Evidence indicates that 82% of complications associated with PPIs are seen in patients with preexisting risk factors, highlighting the need for tailored prescribing of PPIs.⁷ Alarming, more than two-thirds of patients continue PPI therapy after discharge from the hospital without valid justification.

Clinicians are recommended to follow best practices, including prescribing intermittent therapy at the lowest effective dose. Suggested durations of PPI therapy are 4–8 weeks for GERD and peptic ulcers, 10–14 days for *Helicobacter pylori* eradication, up to 12 months for short bowel syndrome, and 12 weeks (extendable to 6 months) for high-risk NSAID users to minimize ulcer risk. In some cases, such

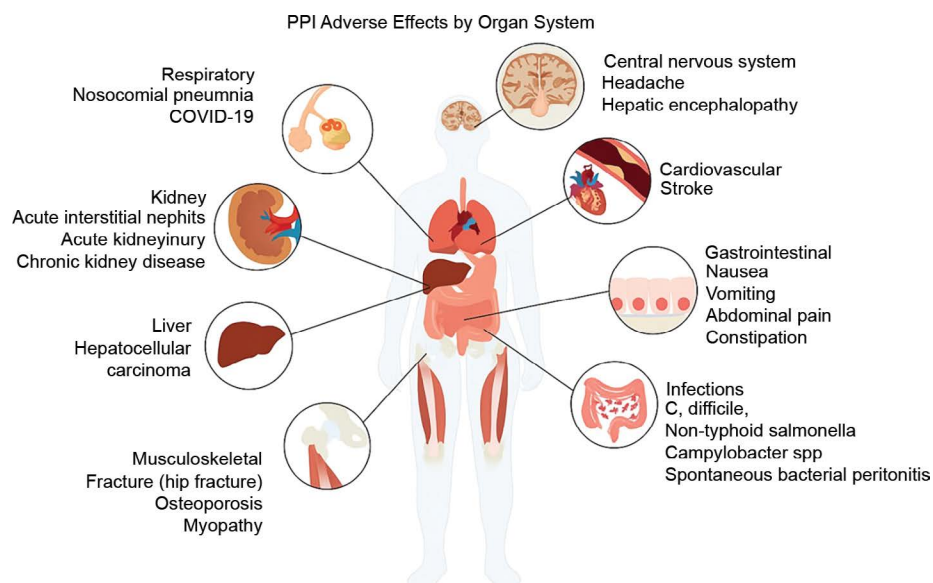
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Table 1: Extended PPIs therapy and its risks with their proposed mechanisms⁹

S. No.	Adverse effect	Proposed mechanism(s)
1	Renal complications	Accumulation of PPI in the tubulo-interstitium → immune-mediated interstitial inflammation → acute interstitial nephritis (AIN) → progression to acute kidney injury (AKI) → chronic interstitial fibrosis → CKD → end-stage renal disease (ESRD)
2	Cardiovascular risks (myocardial infarction, stroke)	Increased asymmetric dimethylarginine (ADMA) → reduced nitric oxide → endothelial dysfunction; reduced vitamin C and B12 levels; enhanced oxidative stress
3	Fractures	Impaired calcium absorption due to insoluble calcium salts in hypochlorhydric conditions and PPI-induced hypergastrinemia
4	Infections (<i>C. difficile</i> , community-acquired pneumonia)	Suppressed gastric acid → diminished barrier function → increased bacterial colonization with subsequent overgrowth in the GI tract
5	Micronutrient deficiencies (Mg ²⁺ , Iron, and vitamin B12)	Reduced acid-dependent mineral absorption, altered transporter activity, and gut microbiota dysbiosis
6	Hypergastrinemia	Chronic suppression of gastric acid → persistent stimulation of G-cells → elevated gastrin secretion
7	Cancer risk (GIT and hepatic cancer)	Long-term acid suppression → enterochromaffin-like (ECL) cell hyperplasia, bacterial overgrowth, and hypergastrinemia
8	Hepatic encephalopathy	Reduced gastric acid → impaired absorption of vitamin B12, magnesium, and iron; increased β -amyloid accumulation
9	Type 2 diabetes mellitus	Altered gut microbiota, magnesium depletion, reduced incretin response, and weight gain

**Fig. 1:** PPI therapy-associated adverse effects¹⁰

as after lung transplantation, long-term or indefinite use may be necessary.⁸ PPIs are not advised for infants because of limited efficacy and safety data. Dosing should always be conservative to lower the risk of complications.

LONG-TERM CONSEQUENCES OF PROTON PUMP INHIBITOR THERAPY

Excessive use of PPIs has become a growing concern, highlighting the need to understand their potential long-term adverse outcomes. Over the last decade, several complications linked to prolonged PPI therapy have been documented. Recent studies increasingly

report significant associations between extended PPI use and conditions such as type 2 diabetes mellitus (T2DM), metabolic syndrome, cognitive decline, including dementia, vitamin B12 deficiency, and an elevated risk of bone fractures in adults (Tables 1 and 2; Fig. 1).

INFECTIONS

Clostridioides difficile Infection

Numerous studies have explored the potential link between PPIs and infections, particularly *Clostridioides difficile* infection (CDI)¹¹ and pneumonia.¹² PPIs may disrupt the balance of gut flora, thereby fostering an environment conducive to the development

of various infections. Gastric hydrochloric acid acts as a primary defense and neutralizes pathogens present in ingested food or accidentally swallowed bacteria. Long-term suppression of stomach acid through PPI therapy compromises this barrier, permitting microbes to survive and multiply in the gastrointestinal system. PPIs raise gastric pH, creating conditions favorable for gut microbial growth, promoting bacterial translocation, and influencing anti-inflammatory and immune-regulatory functions.¹³

A meta-analysis conducted by Deshpande et al. reviewed 30 studies across 29 journals and reported that PPI therapy is associated with a doubled risk of CDI.¹¹ Additional research carried out in hospital settings further supported this association, revealing a significant increase in CDI cases among general ward patients receiving PPI therapy.¹⁴ In a study by Lewis et al., hospital-acquired CDI incidence and severity outcomes were analyzed between patients receiving PPIs and those who were not. The findings demonstrated that PPI use correlated with a higher frequency and greater severity of hospital-acquired CDI.¹⁵ Moreover, a retrospective observational study indicated that prolonged PPI use was linked with a high risk of CDI, with PPIs posing a greater threat than histamine-2 receptor antagonists (H2RAs).¹⁶ Within pediatric populations, PPIs also showed a stronger association with CDI and recurrent infections when compared with H2RAs.¹⁷ In response to these findings, the Food and Drug Administration (FDA) has issued warnings about the potential association between the use of PPIs and CDI. It advises that patients taking PPIs who develop

Table 2: PPI-related adverse events: mechanism and their effects

Mechanism	Effect
Clostridium difficile infection	
↑ Gastric pH	↓ Acid barrier → <i>C. difficile</i> spores survive
Altered gut microbiota	↓ Colonization resistance → spore germination
Antibiotic synergy	↑ Combined risk of CDI
↓ Immune response (theoretical)	↓ Host clearance of <i>C. difficile</i> and its toxins
Community-acquired pneumonia	
Hypochlorhydria	PPIs suppress gastric acid, reducing the stomach's natural barrier to ingested pathogens
Bacterial overgrowth in upper GI tract	Pathogens like <i>S. pneumoniae</i> and <i>Haemophilus influenzae</i> may colonize the oropharynx and esophagus
Microaspiration	Overgrown gastric contents can be aspirated into the lungs, especially during sleep, leading to CAP
Impaired immune function	Long-term PPI use may affect neutrophil and macrophage function, although this is less clearly proven
Vitamin B12 deficiency	
In food, vitamin B12 is attached to proteins and is liberated through the action of gastric acid	Suppression of gastric acid by PPIs limits the release of vitamin B12 from ingested food
In the stomach, free B12 complexes with intrinsic factor, enabling absorption in the ileum	Chronic hypochlorhydria reduces IF activity and alters gastric environment
Hypomagnesemia	
↑ Gastric pH (from PPI)	↓ Mg salt solubilization
↓ TRPM6/TRPM7 activity	↓ Active Mg absorption in intestine
↓ Mg absorption	Chronic hypomagnesemia
(Rare) renal Mg loss	Contributes in susceptible individuals
Osteoporosis	
↓ Stomach acid	↓ Calcium absorption
Hypomagnesemia	Impaired PTH and bone regulation
Hypergastrinemia	↑ Bone resorption
↓ Vitamin B12	↑ Homocysteine → weak bone matrix
Potential direct bone cell effects	Possible ↓ bone formation
Reduced TRPM 7 channel protein expression	Reduced bone proliferation
Dementia	
↓ Gastric acid → ↓ B12	Cognitive decline, ↑ homocysteine
↓ Mg ²⁺ and Fe absorption	Neuronal dysfunction, poor neurotransmission
↑ β-amyloid production	Alzheimer-like pathology
Microbiota alteration → inflammation	Neuroinflammation, cognitive decline
↓ Choline acetyltransferase	↓ Acetylcholine → memory impairment
Kidney impairment	
Acute interstitial nephritis	Tubular damage → interstitial fibrosis
Hypomagnesemia	Tubular injury, nephrocalcinosis
Oxidative stress	Endothelial damage → glomerulosclerosis
Altered microbiome	Uremic toxin accumulation
Volume depletion	Ischemic injury → CKD progression

persistent diarrhea ought to be investigated for possible *C. difficile*-associated diarrhea (CDAD).¹⁸

Pneumonia

The characteristics of pneumonia include inflammation of the lung tissue, often resulting in fluid or pus accumulation in the alveoli. The most common bacterial pathogens responsible for pneumonia include *Streptococcus pneumoniae* and *Mycoplasma*

pneumoniae. A growing body of research has suggested an association between the use of PPIs and the diagnosis of pneumonia. In October 2011, the American College of Chest Physicians (ACCP) conducted a meta-analysis comprising 1,20,863 pneumonia cases reported between 1987 and 2006 to explore this association, focusing specifically on community-acquired pneumonia (CAP). The analysis, which considered variables such as PPI dose, duration, and timing of

use, concluded that PPIs were significantly associated with an increased risk of CAP.¹⁹

Another systematic review involving 33 studies further examined the risk of CAP among outpatient PPI users. The findings showed a 1.49-fold increase in CAP risk, regardless of age or PPI dosage, with the highest risk occurring within the first month of initiating therapy. PPI use also correlated with a greater likelihood of hospitalization due to CAP during this early treatment period.²⁰

The underlying mechanisms proposed for this association include a reduction in gastric acidity, which diminishes the stomach's defense against ingested pathogens. This altered environment facilitates bacterial survival and potential colonization of the upper gastrointestinal tract, increasing the chance of aspiration. Additionally, changes in the oropharyngeal and gastric microbiota, coupled with impaired immune responses such as neutrophil dysfunction, may further elevate the risk.

Research indicates that the likelihood of developing CAP is nearly three times higher in individuals who begin PPI therapy within 30 days. Although the oropharyngeal bacterial profile remained similar among current, former, and nonusers of PPIs, users were more frequently diagnosed with infections caused by *S. pneumoniae*, which contributes to the observed rise in CAP cases.^{21,22}

Another meta-analysis involving nearly 10 lakh participants supported the connection between PPI use and CAP, with new users of PPIs having a twofold higher risk of CAP than those not using the medication.²³ In a primary care cohort of 75,050 individuals aged 60 years and above, those on a 1-year PPI regimen demonstrated a heightened risk of developing pneumonia in the subsequent years following initiation of the medication, with this pattern being consistent across various age and comorbidity groups.²⁴ Altogether, CAP is increasingly recognized as a possible adverse outcome associated with prolonged or inappropriate PPI use.

NUTRITIONAL DEFICIENCY

Vitamin B12 Deficiency

Vitamin B12 is necessary for the proper functioning of the central nervous system, myelin formation, red blood cell synthesis, and DNA replication.²⁵ It also acts as an important cofactor involved in fatty acid as well as amino acid metabolism during DNA synthesis. The leading cause of vitamin B12 deficiency is malabsorption, typically resulting from insufficient intrinsic factor or reduced acid-pepsin activity, such as in cases of hypochlorhydria.²⁶ Vitamin B12 absorption involves a two-step process. In the first stage, hydrochloric acid in the stomach helps release vitamin B12 from dietary proteins. In the next stage, intrinsic factor (a glycoprotein necessary for its absorption in the ileum) attaches to vitamin B12 for absorption.²⁷ Consequently, long-term suppression of gastric acid by PPIs may hinder this process, elevating the likelihood of developing vitamin B12 deficiency.²⁸

This risk is particularly pronounced among older adults. Prolonged use of PPIs is linked with declining vitamin B12 levels in geriatric populations.²⁹ For example, institutionalized elderly individuals taking PPIs for 1 year exhibited a significant reduction in vitamin B12 levels compared with those not using the drugs.³⁰ Moreover, when PPIs are used in combination with medications such as metformin, the reduction in vitamin B12 levels can be more pronounced.²⁸ A study examining older adults showed a strong association between chronic use of PPIs and histamine-2 receptor antagonists (H2RAs) and vitamin B12 deficiency, which may manifest through hematologic, neurological, and psychiatric symptoms. However, this association was not observed with short-term PPI use. Collectively, chronic PPI use can interfere with vitamin B12 absorption, potentially resulting in clinically significant deficiency, particularly in elderly populations.³¹

Hypomagnesemia

A study exploring the association between chronic PPI use and hypomagnesemia identified two cases in which individuals developed severe deficiencies of magnesium, potassium, and calcium. These symptoms improved after the discontinuation of PPI therapy, highlighting a potential causal relationship.³² A large cohort study involving 9,818 participants demonstrated that PPI users were twice as likely to develop hypomagnesemia compared with those not taking PPIs. The risk further increased when PPIs were used alongside loop diuretics, suggesting a compounding effect.³³ Interestingly, switching to a different PPI did not alleviate the hypomagnesemia, indicating a class effect across all PPIs. According to the Food and Drug Administration Adverse Event Reporting System (FAERS), pantoprazole presented the highest association with hypomagnesemia, while esomeprazole had the lowest. The data also showed that older individuals and males were more susceptible to this adverse effect, and cases of PPI-induced hypomagnesemia were frequently accompanied by concurrent hypokalemia and hypocalcemia. Females, in contrast, exhibited a significantly lower risk of developing hypomagnesemia.³⁴

In another study comparing hospitalized adults on PPIs with nonusers, the average magnesium level measured in PPI users was 1.19 mg/dL, compared with 2.0 mg/dL in those not using PPIs. Even after adjusting for confounding variables, the likelihood of hypomagnesemia remained approximately doubled in those receiving PPIs.³⁵ The risk

of developing hypomagnesemia increases with higher PPI dosages. Severe magnesium deficiency due to PPI therapy has the potential to cause severe neuromuscular and cardiac issues, often presenting in combination with low calcium and potassium levels.³⁶ Magnesium uptake occurs through two pathways: passive diffusion and an active transport mechanism within the gastrointestinal tract. Active absorption is primarily mediated by transient receptor potential melastatin 6 and 7 (TRPM6 and TRPM7) channels, which are present on the apical membrane of enterocytes. These channels facilitate the movement of magnesium into the bloodstream. However, PPIs may alter intestinal pH levels, potentially impairing the function of TRPM6/TRPM7 channels and disrupting magnesium transport. As a result, prolonged PPI use can hinder both active and passive absorption of magnesium, contributing to hypomagnesemia.³⁷

Hypocalcemia and Hypokalemia

Evidence from over 10 million adverse event submissions available in the Food and Drug Administration Adverse Event Reporting System (FAERS) suggests a significant link between PPI use and electrolyte disturbances such as hypocalcemia and hypokalemia. Prolonged PPI therapy may impair calcium absorption, predisposing patients to hypocalcemia. In addition, hypokalemia observed in PPI users may be secondary to PPI-induced chronic kidney disease (CKD).³⁸

Anemia

Several case reports and observational studies have documented PPI-associated anemia. Multiple mechanisms have been proposed, including impaired iron absorption resulting from PPI-induced hypochlorhydria.³⁹ Furthermore, PPIs may reduce iron availability by increasing the expression of hepcidin, a peptide hormone that regulates iron homeostasis and inhibits duodenal ferroportin-mediated iron export.⁴⁰

OSTEOPOROSIS AND FRACTURE

Skeletal complications, including osteoporosis and fragility fractures, remain an important concern with chronic use of PPIs. A large population-based study in Canada reported an elevated risk of nontraumatic fractures among chronic PPI users. Notably, this association persisted even after adjusting for traditional risk factors such as femoral neck bone density, suggesting that PPI therapy independently contributes to an increased incidence of fragility fractures in both men and women.⁴¹

PPI-induced achlorhydria decreases calcium solubility, thereby impairing its absorption.⁴² Prolonged use of PPIs, particularly beyond 7 years, has been strongly associated with osteoporosis-related fractures, while use exceeding 5 years is linked to an elevated risk of hip fracture.⁴³ Among postmenopausal women, PPI therapy has been correlated with a significant increase in osteoporosis risk. According to the Women's Health in Lund Area (WHILA) study, use of PPIs was associated with a nearly twofold rise in osteoporosis risk and premature fractures during extended monitoring.⁴⁴ Similarly, a German cohort study revealed that the risk of osteoporosis and associated fractures escalates with the duration of PPI treatment, further emphasizing a time-dependent relationship.⁴⁵

A multicenter Canadian osteoporosis study reported that individuals using PPIs exhibited lower baseline bone mineral density (BMD), particularly at the neck of the femur and total hip, compared with those not using PPIs. However, PPI use did not significantly influence the rate of BMD loss over time. Nonetheless, prolonged PPI therapy used at higher doses has been associated with a heightened risk of hip fractures.^{46,47}

The profound reduction in stomach acid caused by PPIs, particularly among older adults, can impair calcium absorption, a critical factor for bone health.⁴⁸ Various other studies have demonstrated that PPI treatment may hinder calcium uptake and contribute to reduced bone density.⁴⁹ Although PPIs reduce bone resorption by inhibiting osteoclastic vacuolar-type H⁺-ATPase pumps, they also compromise calcium absorption because of the hypochlorhydric environment they create.⁴⁷

A meta-analysis suggested that PPI users faced a 26% higher risk of hip fractures relative to those who did not use these medications. Several epidemiological investigations have similarly linked PPI therapy to a higher occurrence of hip fractures.^{47,50} Further insight into the mechanism was provided by research into the transient receptor potential melastatin 7 (TRPM7) channel, which is expressed in osteoblasts as well as osteoclasts and plays a vital role in bone development. An *in vitro* study examining pantoprazole's effect on TRPM7 demonstrated dose-dependent inhibition of cell viability and a reduction in TRPM7 protein expression in both osteoblastic and osteoclastic cells.⁵¹ This suggests that PPIs may negatively impact bone remodeling by disrupting cellular pathways essential to bone turnover.⁵²

Moreover, extended use of PPIs has repeatedly been correlated with an increased

fracture risk involving the hip, spine, and wrist. This elevated risk may stem from reduced calcium solubility and absorption secondary to hypochlorhydria, as well as hypergastrinemia induced by long-term acid suppression.⁵³ A meta-analysis encompassing 11 studies suggested a modest increase in fracture incidence at various anatomical sites among PPI users, reinforcing the link between prolonged PPI therapy and skeletal fragility.⁵⁴

DEMENTIA

Dementia encompasses a wide range of conditions, with Alzheimer's disease accounting for the largest proportion of cases among the elderly. Several studies have indicated a potential link between chronic use of PPIs and a heightened risk of dementia and Alzheimer's disease in the elderly.⁵⁵ A review study has also identified a strong association between the use of PPIs and cognitive decline.⁵⁶ National Health and Nutrition Examination Survey (NHANES) data (1999–2012) reported a notable rise in PPI prescriptions among US adults aged 40–60 years, increasing from 4.9 to 8.3%. This growing trend, particularly among the aging population, has raised safety concerns because of possible cognitive side effects.⁵⁷ Evidence suggests that elderly individuals regularly taking PPIs may face a significantly higher risk of developing dementia.⁵⁸

A pharmacoepidemiologic cohort study compared dementia risk among users of histamine-2 receptor antagonists (H2RAs) and PPIs with nonusers. Results indicated that both medication groups were associated with an increased incidence of dementia.⁵⁹ Several mechanisms have been proposed to explain this relationship. For instance, *in vitro* research has shown that chronic use of PPIs may impede the clearance of amyloid beta (Aβ), a hallmark of Alzheimer's pathology. Microglial elimination of fibrillary Aβ requires proper lysosomal acidification, a process disrupted by PPI-mediated inhibition of V-ATPase proton pumps, leading to reduced Aβ degradation and accumulation.⁶⁰

Additionally, PPIs are inverse modulators of γ-secretase while also enhancing the activity of β-site amyloid precursor protein-cleaving enzyme 1 (BACE1), both of which are involved in Aβ production and plaque formation.⁶¹ Another contributing factor is vitamin B12 deficiency, commonly associated with prolonged PPI use. This deficiency can impair cognitive function by disrupting DNA synthesis and methylation pathways and by increasing neurotoxic homocysteine levels.⁶² Vitamin B12 is essential for one-carbon metabolism, supporting the synthesis

of neurotransmitters, phospholipids, and nucleotides. A deficiency can lead to hyperhomocysteinemia, which, along with reduced methylation, has been implicated in dementia and Alzheimer's disease. Elevated homocysteine levels and impaired methylation may also reduce protein phosphatase 2A activity, promoting tau protein hyperphosphorylation and aggregation, a key feature of Alzheimer's pathology.^{63–65}

Animal model studies have further supported these findings, demonstrating that PPI treatment increases brain Aβ levels by modulating β- and γ-secretase activity⁶⁶ and contributes to vitamin B12 deficiency, which has been correlated with cognitive dysfunction.⁶¹ Moreover, PPIs inhibit choline acetyltransferase, which reduces the synthesis of acetylcholine, a neurotransmitter critical for learning and memory.⁶⁷ A reduction in acetylcholine production can significantly affect cognitive performance, increasing the risk of dementia. Overall, current evidence indicates a concerning link between long-term PPI use and the onset of dementia.⁶⁸ This highlights the necessity of monitoring chronic PPI administration, especially in older adults, by weighing the therapeutic benefits against potential cognitive risks.

KIDNEY DISEASES

A potential causal relationship has been found between the utilization of PPIs and the development of CKD.⁶⁹ A study identified an independent correlation between PPI therapy and a 20–50% elevation in the risk of CKD. Notably, the study indicated that PPI therapy alone could be a contributing factor to kidney dysfunction.⁷⁰ The association was more clearly demonstrated in patients aged 18 years and above with no previous history of kidney disease. When these individuals initiated PPI therapy and were followed longitudinally, they exhibited a significantly increased frequency of acute kidney injury compared with those not taking PPIs.⁷¹ Extended PPI therapy has been associated with a 1.3-fold higher likelihood of developing CKD or advancing to end-stage renal disease (ESRD), relative to those treated with histamine-2 receptor antagonists (H2RAs). Importantly, such a correlation was not found in the H2RA group, indicating a distinct risk pattern unique to PPI exposure.⁷² Various clinical trials related to PPI-associated kidney impairment are shown in Table 3.

Several studies have investigated the underlying mechanisms through which PPIs may lead to kidney function decline. One proposed pathway involves PPI-

Table 3: Evidence linking PPIs with renal and vascular complications⁷³

Study	Study characteristics	Key outcome
Lee et al., 2018	Included patients >18 years who received PPIs for 1–2 years	PPI use was longer in patients with CKD compared to non-CKD patients
Fusaro et al., 2013	Evaluated aortic and iliac artery calcification among PPI users	PPI utilization was significantly associated with increased arterial calcifications
Giusti et al., 2021	Utilized the US Veterans Affairs database to assess PPI use and kidney function decline	PPI use accelerated kidney dysfunction; hazard ratio 1.82 with 95% CI: 1.53–2.9

induced hypomagnesemia, which can lead to increased renal calcification.⁷⁴ In patients undergoing hemodialysis, chronic PPI use has been associated with a higher incidence of vascular calcification. Magnesium serves as a natural inhibitor of calcification, so a PPI-related reduction in magnesium levels may exacerbate vascular calcification, particularly in individuals with CKD. Another well-documented mechanism is characterized by the emergence of acute interstitial nephritis (AIN) triggered by PPI use.⁷⁵ The metabolites of PPIs may function as haptens,⁷⁶ binding with larger peptides and contributing to immune complex formation, which is later deposited within renal tubular structures. This stimulates an immune response, predominantly mediated by T cells, which release inflammatory cytokines and chemotactic agents that contribute to interstitial inflammation and kidney injury.⁷⁷

CARDIOVASCULAR COMPLICATIONS: MYOCARDIAL INFARCTION AND STROKE

The use of PPIs has been associated with increased concentrations of asymmetric dimethylarginine (ADMA), which suppresses nitric oxide synthase activity. PPI therapy may interfere with the normal functioning of dimethylarginine dimethylaminohydrolase (DDAH), thereby increasing circulating ADMA concentrations. This imbalance reduces nitric oxide (NO) bioavailability, resulting in heightened vascular tone, impaired vasodilation, and a predisposition to cardiovascular adverse outcomes, including myocardial infarction (MI) and ischemic stroke.⁷⁸

Clinical evidence supports this proposed mechanism. A cohort study involving 27,624 participants without prior ischemic heart disease revealed that chronic or high-dose exposure to PPIs was significantly linked with the onset of acute MI.⁷⁹ Furthermore, chronic PPI use has been statistically correlated with cerebral small vessel disease, particularly deep white matter disease, as revealed through multivariate Cox regression, which

is a well-recognized precursor of stroke and cognitive decline.⁸⁰

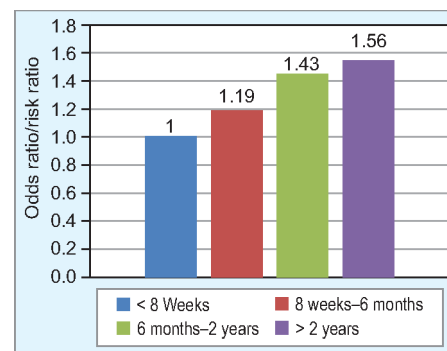
Large population-based studies corroborate these findings. A Danish nationwide cohort study of nearly 214,000 individuals reported that sustained PPI therapy was associated with a greater incidence of primary ischemic stroke and myocardial infarction.⁸¹ Similarly, retrospective cohort data from Taiwan showed that PPI therapy was associated with higher rates of hospitalization for ischemic stroke.⁸²

METABOLIC SYNDROME AND TYPE 2 DIABETES MELLITUS

Several studies have demonstrated an association between long-term PPI use and an elevated likelihood of developing type 2 diabetes mellitus (T2DM) and metabolic syndrome. A large retrospective study including 7,774,29 new PPI users identified 50,535 patients with diabetes and compared them with matched controls by age, sex, and clinical characteristics, revealing an association between PPI therapy and the development of diabetes.⁸³

The risk appears to be duration-dependent. Patients receiving PPIs for durations between 8 weeks and 2 years exhibited a higher incidence of diabetes than those exposed for shorter durations (Fig. 2).⁸³ Furthermore, frequent PPI users showed a 24% greater chance of developing diabetes relative to nonusers, with the risk escalating progressively with prolonged treatment. This finding has been consistently validated in three large prospective cohort studies.⁸⁴

In another investigation, research found that 73.9% of elderly patients were inappropriately prescribed PPIs. The excessive prescribing was strongly associated with underlying cardiac and metabolic conditions, underscoring concerns about the overutilization of these medications in elderly individuals with multiple comorbidities.⁸⁵ One of the mechanisms potentially connecting PPI use to diabetes is PPI-induced hypomagnesemia.⁸⁶ Hypomagnesemia is repeatedly observed to worsen blood

**Fig. 2:** Relationship between PPI duration and odds ratio (risk ratios)⁷³

glucose control in patients with type 1 as well as type 2 diabetes. Magnesium supplementation has been demonstrated to enhance insulin sensitivity while lowering insulin requirements. In one study, diabetic individuals receiving 250 mg of magnesium hydroxide twice daily showed reduced insulin requirements compared with healthy controls.⁸⁷ Similarly, another case-control study involving 200 subjects suggested that magnesium depletion in obese patients with diabetes is influenced by the degree of metabolic control.⁸⁸

Four weeks of oral magnesium administration in elderly patients with type 2 diabetes led to reduced fasting glucose levels, increased intracellular magnesium, and a modest but statistically significant improvement in pancreatic β -cell responsiveness. These findings suggest that chronic magnesium deficiency, possibly exacerbated by PPI use, may impair glucose metabolism, insulin signaling, and overall glycemic control.⁸⁹ Additional studies have linked hypomagnesemia in diabetic individuals with complications such as retinopathy, nephropathy, and diabetic foot ulcers.⁹⁰ Mather et al. found hypomagnesemia in approximately 25% of the diabetic patients studied.⁹¹ Given that PPIs may contribute to or worsen magnesium deficiency, there is a plausible link between their use and impaired glycemic control. This underscores the need for ongoing monitoring of both diabetic and nondiabetic individuals on long-term PPI therapy.

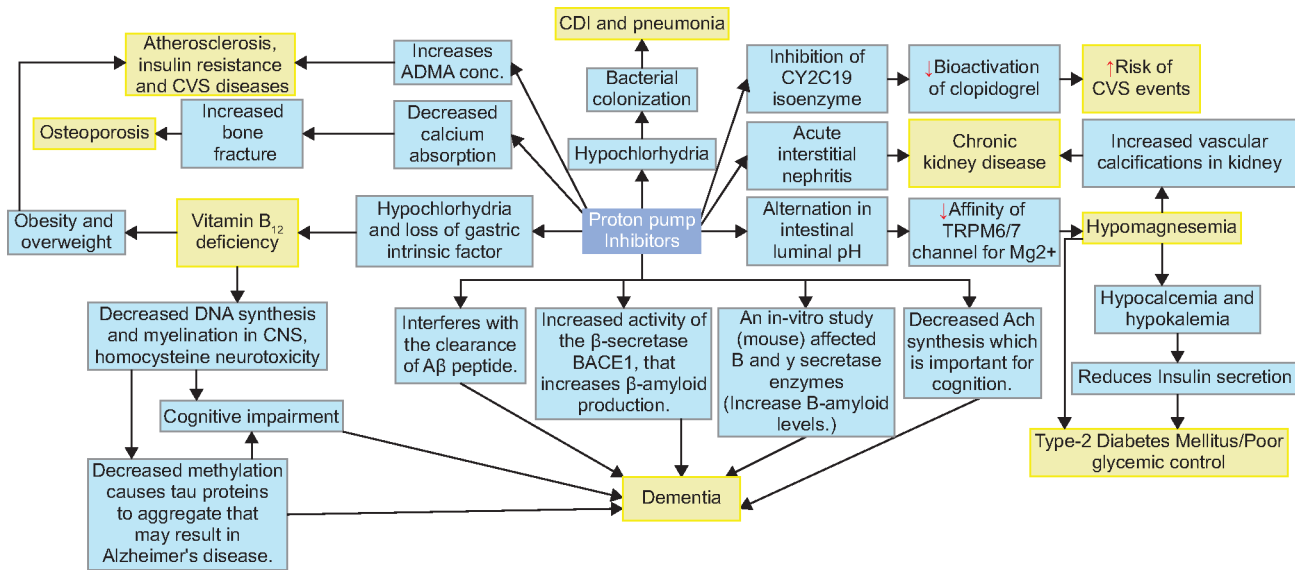


Fig. 3: Cascade of adverse outcomes associated with long-term PPI use⁷³

Nitric Oxide, Asymmetric Dimethylarginine, and Cardiovascular Risk

Nitric oxide (NO), a critical molecule synthesized by endothelial cells *via* endothelial nitric oxide synthase (eNOS), plays a fundamental role in maintaining vascular health.⁹² It regulates vascular tone, inhibits platelet aggregation, and limits leukocyte adhesion, making it essential for cardiovascular protection.⁹³ Asymmetric dimethylarginine (ADMA) is a naturally occurring inhibitor of eNOS, and elevated levels have been linked to increased cardiovascular risk.⁹⁴ PPIs have been shown to raise plasma levels of ADMA by inhibiting dimethylarginine dimethylaminohydrolase (DDAH), the enzyme responsible for its degradation. This inhibition reduces NO synthesis, impairs endothelium-dependent vasodilation, and contributes to vascular dysfunction. Because individuals with diabetes already tend to have higher ADMA levels, the addition of PPI therapy may exacerbate their cardiovascular risk.⁹⁵

Secondary Hypergastrinemia and Other Long-term Risks

Chronic PPI use suppresses gastric acid secretion, resulting in compensatory hypergastrinemia. Elevated gastrin levels stimulate enterochromaffin-like (ECL) cell proliferation, potentially increasing the risk of gastric carcinoid tumors and various histopathological modifications in the gastric lining. Moreover, this persistent elevation may trigger rebound acid hypersecretion when PPI therapy is discontinued, complicating the management of acid-related disorders. Extended PPI therapy has also been linked with a variety of other complications, including

an increased risk of infections, nutrient deficiencies (notably calcium, magnesium, and vitamin B12), and osseous fractures, especially in geriatric individuals or those with underlying liver disease.

Given these risks, medical professionals are urged to adopt judicious prescribing practices. Trials such as STOPPIT have explored the outcomes of deprescribing PPIs in high-risk groups. Alternative approaches, including the use of histamine-2 receptor antagonists (H2RAs), lifestyle changes, or step-down strategies, are recommended to reduce long-term PPI dependence while maintaining effective symptom control. Routine reevaluation of the need for PPI therapy, informed by clinical guidelines and patient-specific factors, is vital for achieving better outcomes and lowering the likelihood of adverse effects (Figs 3 and 4).

EXPLORING THE CONNECTION BETWEEN EXTENDED PROTON PUMP INHIBITOR THERAPY AND CANCER SUSCEPTIBILITY

Emerging evidence suggests that extended PPI therapy has been linked to a potentially higher risk of several cancers, such as gastric, pancreatic, colorectal, and liver malignancies. A comprehensive umbrella review of 21 meta-analyses, covering 65 observational studies, found that PPI use is associated with a statistically significant higher risk of these cancers.⁹⁷

Gastric Cancer

Multiple studies identified a positive correlation between chronic PPI use and the development of gastric cancer. Prolonged exposure to PPIs has been linked

to more than double the risk of gastric cancer. Potential mechanisms include profound acid suppression, which can contribute to gastric atrophy, chronic hypergastrinemia, enterochromaffin-like (ECL) cell hyperplasia, and bacterial overgrowth, all of which may contribute to carcinogenesis in the gastric mucosa.⁹⁸ An analytical study demonstrated a notable link between chronic PPI therapy and the development of fundic polyps as well as gastric cancer.⁹⁹ Another large-scale meta-analysis involving 9,26,386 individuals reported a twofold higher risk of gastric cancer among chronic users of PPIs.¹⁰⁰

Pancreatic Cancer

A nationwide study conducted using the French National Health Data System (SNDS) found that chronic PPI use was associated with an increased risk of pancreatic cancer. The hypothesized mechanisms include hypergastrinemia and bacterial overgrowth associated with reduced gastric acidity, both of which may create a microenvironment conducive to pancreatic tumor development.¹⁰¹

Colorectal Cancer

Extended PPI therapy has also been implicated in a higher likelihood of developing colorectal malignancy. A Swedish population-based cohort study found that long-term PPI users had higher rates of both all-cause and colorectal cancer-specific mortality.¹⁰² Mechanistically, chronic PPI use may contribute to hypergastrinemia, which promotes proliferation of colonic and rectal epithelial cells. Additional factors such as activation of the Yes-associated protein (YAP), disruption of the gut microbiota, and increased fecal pH may also play roles in colorectal tumorigenesis.¹⁰³

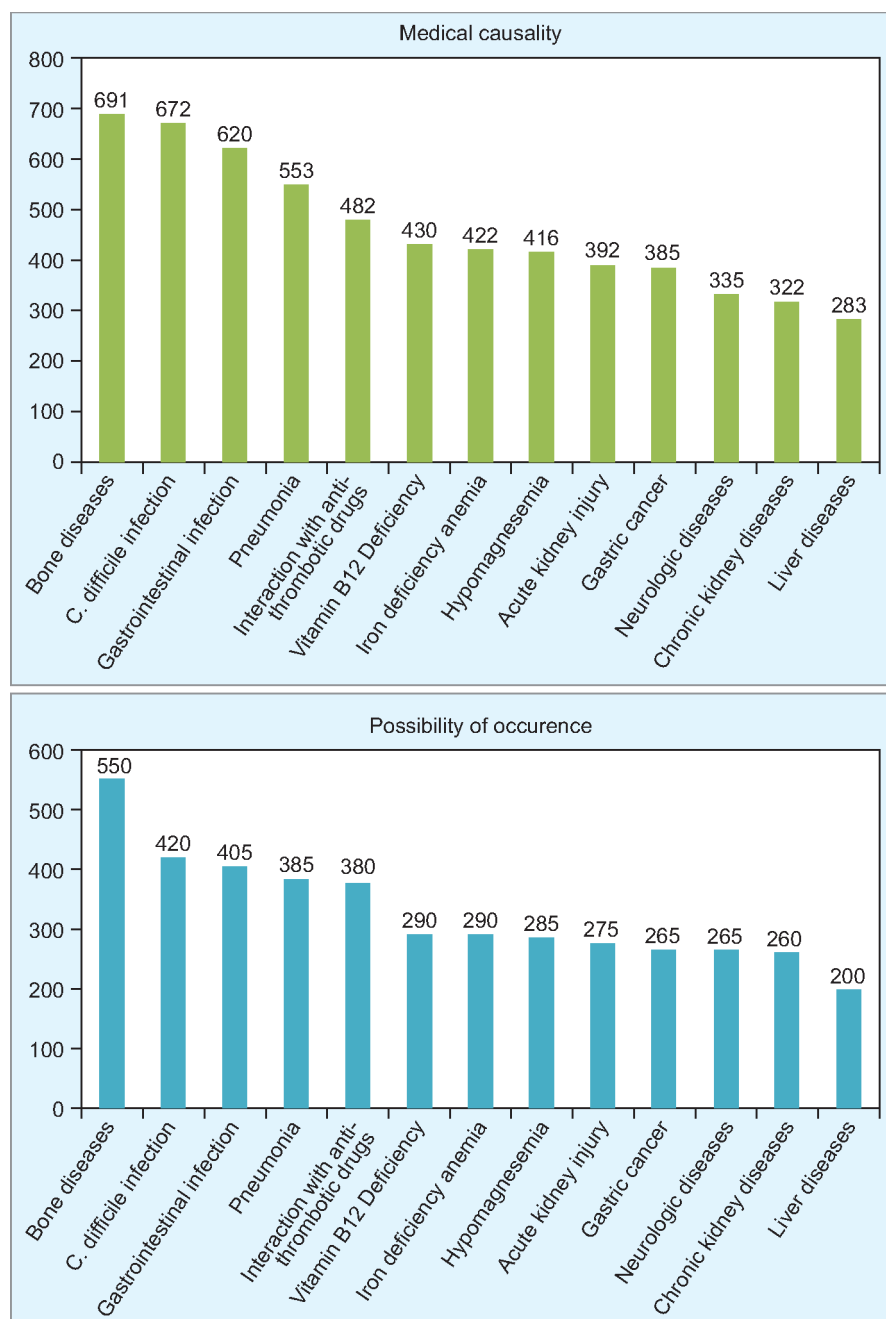


Fig. 4: Assessment of clinical causation and the likelihood of occurrence of established major adverse effects associated with PPIs⁹⁶

Hepatic Cancer

Prolonged PPI use may increase the likelihood of developing hepatocellular carcinoma (HCC), particularly in patients with preexisting liver disease. An analysis of 11 studies suggested that PPI use in individuals with chronic liver disease was associated with a significantly elevated risk of developing HCC and increased mortality. The underlying mechanism may again involve sustained hypergastrinemia, which has been associated with hepatic cellular proliferation and oncogenesis.¹⁰⁴

CONCLUSION

Although PPIs are widely accessible and commonly prescribed, their long-term use has been linked with a range of potentially serious adverse effects. Reported complications include osteoporosis, CDI, respiratory infections such as pneumonia, magnesium deficiency, CKD, vitamin B12 deficiency, and type 2 diabetes mellitus (T2DM). These health risks not only pose significant clinical concerns but also contribute to increased health care expenditures, placing a financial strain on patients.

Given these risks, it is imperative that clinicians carefully evaluate the necessity of PPI therapy, particularly for prolonged or continuous use. Treatment decisions should be based on a clear and justified indication, and ongoing reevaluation is essential to ensure that continued use remains appropriate. This review highlights the various biological pathways through which PPIs may contribute to adverse outcomes, including their impact on glucose and lipid metabolism in relation to T2DM. Nonetheless, further clinical research is warranted to validate these associations and to determine whether PPI use significantly affects glycosylated hemoglobin (HbA1c), low-density lipoprotein (LDL), and triglyceride levels.

AUTHOR CONTRIBUTIONS

Dr C Nawal and Dr H Saini contributed to the concept and design of this expert opinion document. The manuscript draft was developed by Dr G Rankawat and critically reviewed by all the authors. The manuscript was edited and revised by Dr G Rankawat and Dr R Chejara. The final draft of the manuscript was approved by all contributing authors.

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