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Long-term Proton Pump Inhibitor use and nutritional deficiencies: a narrative mini-review with emphasis on omeprazole and the role of community pharmacy

Abstract

Long-term use of proton pump inhibitors (PPIs) is highly prevalent and often exceeds the duration recommended in clinical guidelines. Although PPIs are effective and generally safe when appropriately prescribed, prolonged or unjustified use has been associated with clinically relevant nutritional and electrolyte alterations in selected patients. This mini-review summarizes evidence on vitamin B12, iron, magnesium and calcium status, as well as fracture risk. The mechanisms proposed include increased gastric pH, impaired mineral solubility and absorption, changes in intestinal transport pathways and possible microbiota-related effects. However, the strength of evidence differs between outcomes, and some associations may be influenced by confounding factors such as age, comorbidity, frailty, concomitant medication and baseline nutritional status. Community pharmacy can contribute to the early identification of patients who may benefit from treatment review through active dispensing, structured screening, health education and referral for medical assessment when deprescribing may be appropriate. Optimizing long-term PPI use may help reduce preventable medicine-related risks while preserving treatment benefits in patients with a valid indication.

Keywords: proton pump inhibitors, nutritional deficiencies, deprescribing, community pharmacy

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Introduction

Proton pump inhibitors (PPIs), including omeprazole, lansoprazole, rabeprazole, pantoprazole and esomeprazole, are among the most frequently prescribed pharmacological groups within the Spanish National Health System and have been among the most widely used medicines in recent years.[1] Their main indications include gastric acid-related disorders, for which they have shown greater efficacy than other anti-ulcer drugs, such as histamine H2-receptor antagonists. PPIs are also indicated for the prevention of non-steroidal anti-inflammatory drug (NSAID)-induced gastroduodenal ulcers in patients at increased risk.[2]

Although PPIs have a favourable safety profile when used for short-term treatment, generally for periods shorter than eight weeks, their use is not always clinically justified. In routine practice, many patients continue treatment for longer than recommended in product information or clinical practice guidelines.

In Spain, PPI prescribing rates are approximately 70% higher than the European average. Around one in ten people takes a PPI daily, a figure considerably higher than that observed in other European countries and not fully explained by the available epidemiological data. This raises concerns regarding both the appropriateness and the duration of these treatments. The issue affects all levels of healthcare. Hospitalization has been identified as a risk factor, since approximately two thirds of inappropriate PPI prescriptions are initiated in the hospital setting.[1,2]

The prolonged continuation of PPI therapy and the widespread perception of these drugs as "gastric protectors" have contributed to inappropriate use. Despite their long history of clinical use, PPIs are not free from adverse effects. Some potential adverse effects may be clinically relevant in susceptible patients, particularly when treatment is prolonged without a clear indication. Therefore, an appropriate assessment of each patient is required across healthcare settings, and deprescribing should be considered whenever treatment is no longer indicated.

Objectives

Primary objective:

To conduct a narrative mini-review of the scientific evidence on nutritional and electrolyte alterations associated with long-term PPI use.

Secondary objectives:

To analyze active dispensing, structured screening, deprescribing and health education as key community-pharmacy strategies for reducing preventable risks related to prolonged or unjustified PPI use.

Materials and methods

A narrative mini-review of the available scientific literature was carried out. Because the aim was to provide a concise and practice-oriented synthesis, no formal systematic review protocol, risk-of-bias assessment or meta-analysis was performed.

Information sources and search date. PubMed, the Cochrane Library, Google Scholar and ScienceDirect were searched. The last search was performed in November 2025. Complementary information from scientific societies was also consulted to contextualise PPI use, appropriateness, and deprescribing and community-pharmacy practice.

Search terms and strategy. The search combined free-text terms related to exposure, outcomes and practice setting. The main terms were: "proton pump inhibitors", "PPI", "omeprazole", "long-term use", "nutritional deficiency", "vitamin B12", "iron deficiency", "hypomagnesemia" or "hypomagnesaemia", "calcium", "fracture", "deprescribing", "active dispensing" and "community pharmacy".

Terms were combined using the Boolean operators AND and OR. Equivalent Spanish terms were also used when searching Spanish sources.

Selection criteria. Priority was given to publications from 2020 to 2025, available in English or Spanish, addressing adults exposed to long-term PPIs and reporting nutritional, electrolyte, bone-related or deprescribing outcomes. Reviews, systematic reviews, meta-analyses, clinical practice recommendations, pharmacoepidemiological studies, primary-care studies and clinically relevant case reports were considered. Publications not focused on PPIs, not related to the outcomes of interest, paediatric studies and sources without sufficient clinical relevance for community pharmacy were excluded after title and abstract screening.

Rationale for older references. Although recent evidence was prioritized, older references were retained when they were directly relevant, frequently cited, mechanistic in nature, or when no more recent equivalent source was identified. This explains the inclusion of reference 7, which provides quantitative evidence on hypomagnesaemia risk and remains relevant for interpreting the current evidence base.

Study selection. Titles and abstracts were screened for relevance. Full texts were reviewed when the abstract did not provide enough information or when the source was considered central to the objectives of the mini-review. The final selection was based on clinical relevance, methodological quality in relation to the review aim, and applicability to community-pharmacy practice.

Results and discussion

I. Vitamin B12

Long-term and high-dose PPI therapy has been associated with vitamin B12 deficiency, particularly in susceptible patients. The proposed mechanism is biologically plausible: sustained acid suppression can reduce the release of protein-bound vitamin B12 from food, potentially impairing its subsequent absorption.

The clinical manifestations of vitamin B12 deficiency are variable and may include haematological abnormalities and neurological symptoms. Elevated homocysteine levels can also be observed in vitamin B12 deficiency and have been associated with vascular and neurodegenerative disorders and cardiovascular risk. However, these outcomes are multifactorial and should not be attributed solely to PPI exposure without considering age, diet, metformin use, malabsorption disorders and baseline nutritional status.[3]

From a community-pharmacy perspective, patients receiving long-term PPIs who are older, frail, polymedicated, vegetarian or vegan, or treated with metformin may warrant closer review and referral for medical assessment if symptoms or laboratory abnormalities suggest vitamin B12 deficiency.

II. Iron

The absorption of non-haem iron is favoured by an acidic gastric environment. By increasing gastric pH, PPIs may reduce iron solubility and impair the absorption of inorganic iron. A systematic review and meta-analysis reported an increased relative risk of iron deficiency among PPI users, with a relative risk of 2.56, and found that patients treated with PPIs tended to have lower iron levels than individuals not receiving this medication class.[4]

Nevertheless, the association between PPIs and iron deficiency should be interpreted cautiously. Iron deficiency is common and may be influenced by dietary intake, menstrual or gastrointestinal blood loss, chronic inflammation, renal disease and other medicines. Therefore, unexplained anaemia or low ferritin in a long-term PPI user should prompt clinical assessment rather than automatic attribution to the PPI.

III. Magnesium

PPI-associated hypomagnesaemia is an uncommon but clinically important adverse effect, particularly after prolonged exposure. It is generally thought to result from impaired intestinal magnesium absorption rather than increased renal loss. PPIs increase gastrointestinal pH, reducing magnesium solubility and potentially decreasing its availability for absorption.

This less acidic environment may interfere with active magnesium transport, particularly mechanisms mediated by TRPM6 and TRPM7 channels, whose activity is pH-dependent. Genetic susceptibility has also been proposed, as some TRPM6 polymorphisms may increase vulnerability to this electrolyte disorder.

Passive transport may also be affected. PPIs can alter tight junctions in the intestinal epithelium, increasing resistance to magnesium passage and impairing paracellular absorption. Long-term PPI use has also been associated with changes in the intestinal microbiota, which may reduce bacterial fermentation processes that normally contribute to colonic acidification and favour magnesium absorption.

Patients at greater risk include older adults, people with diabetes, individuals with renal impairment and those taking medicines that can lower magnesium levels or increase the clinical impact of hypomagnesaemia, such as thiazide or loop diuretics and digoxin.[5–7] In these patients, symptoms such as cramps, weakness, palpitations, arrhythmias, seizures or unexplained hypocalcaemia should prompt referral for medical assessment and laboratory testing.

IV. Calcium status and fracture risk

Some studies have reported an association between long-term PPI use and reduced calcium absorption. This has been linked to gastric achlorhydria and to the pH-dependent ionization of calcium salts from food, which may influence absorption in the duodenum and proximal jejunum. However, the magnitude and clinical relevance of this mechanism remain uncertain. Hypocalcaemia may also occur secondary to PPI-induced hypomagnesaemia, because low magnesium levels can inhibit both the secretion and the action of parathyroid hormone (PTH).[8,9]

Clinically, recent literature focuses more on fracture risk than on hypocalcaemia itself, especially in older adults. This suggests a possible signal of increased overall bone risk, but causality has not been definitively established. Age, frailty, falls, comorbidities, corticosteroid use, osteoporosis, smoking, alcohol intake, vitamin D status and indication bias may act as confounding factors. Therefore, long-term PPI use should be considered one potential contributor to bone risk assessment, not an isolated cause of fractures.[10]

Role of community pharmacy

A. Structured screening and deprescribing of PPIs

Shared responsibility and multidisciplinary collaboration among healthcare professionals involved in the care of patients with chronic conditions are essential to ensure continuity and traceability of treatment. Primary care nurses and community pharmacists, in collaboration with general practitioners or specialists, can establish communication pathways aimed at strengthening treatment adherence, medication review and safe medicine use.[11]

Long-term PPI therapy may be appropriate when there is a clear indication and when the benefit-risk balance is favourable. Therefore, asymptomatic patients without a clear indication for treatment, as well as patients with an appropriate initial indication whose treatment duration exceeds that recommended in the summary of product characteristics or clinical guidelines, may be candidates for review.

Deprescribing should be individualized and supervised by the physician responsible for the patient. Among the possible strategies,

two are particularly common. The first consists of reducing the PPI dose by approximately 50% every one to two weeks and discontinuing treatment once the lowest effective dose has been reached, provided rebound symptoms do not occur. The second consists of progressively increasing the dosing interval, for example to every 48-72 hours, and subsequently considering on-demand treatment or discontinuation when appropriate.[12]

Practical stepwise approach at the community-pharmacy counter

At the pharmacy counter, implementing a structured approach, as shown in Table 1, based on simple questions about treatment duration, therapeutic indication and patient-related risk factors, may be useful for identifying inappropriate PPI use. When a patient meets any of the criteria for review, the community pharmacist should discuss the situation with the patient and, with their agreement, refer them to their physician for assessment of possible deprescribing, treatment modification or laboratory monitoring (Figure 1).

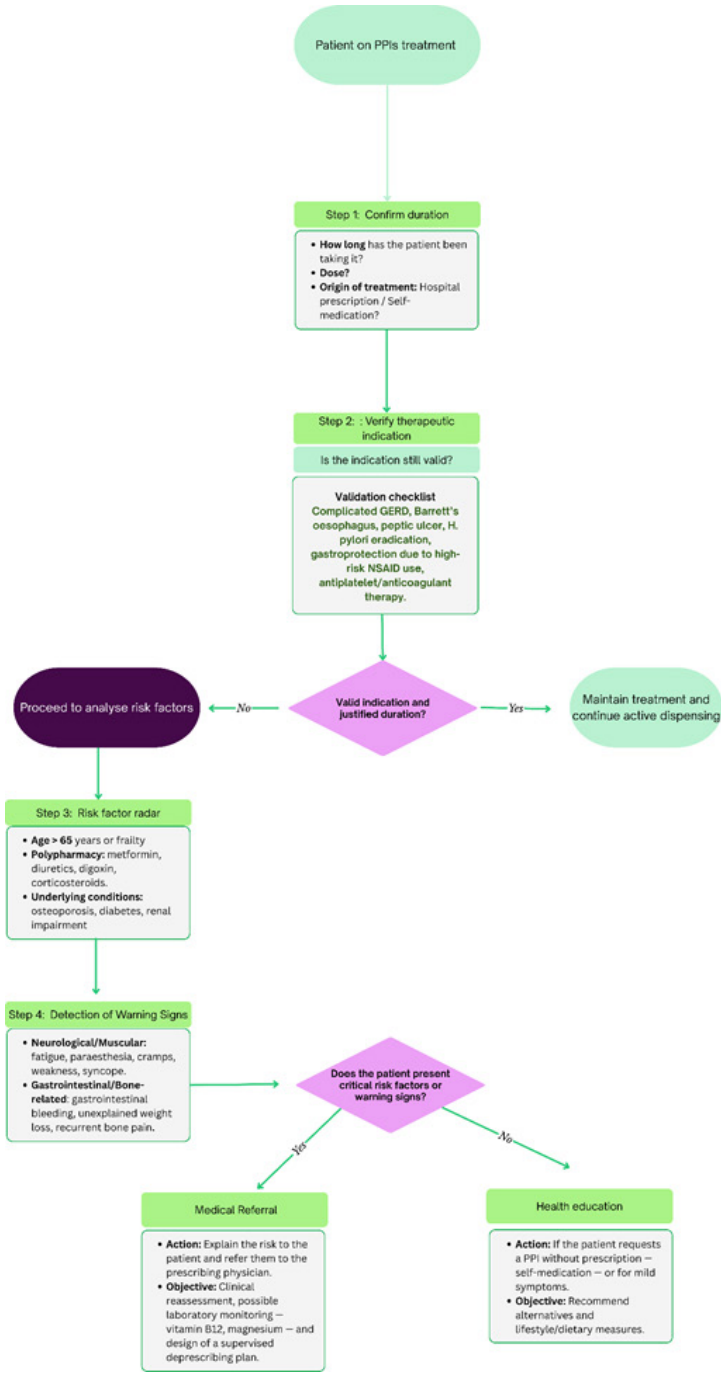

Figure 1 Pharmacy counter decision-making algorithm for patients receiving PPI therapy.

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Table 1 Practical screening approach for identifying patients on proton pump inhibitors who may require medication review in community pharmacy[1,2,11,12]

Step	Pharmacist action	Purpose
Confirm treatment duration	Ask how long the patient has been taking the PPI, the dose, the dosing schedule and whether it was initiated in hospital, primary care or self-medication.	Identify long-term use, high-dose treatment, duplicate therapy and potential inappropriate continuation.
Verify the indication	Ask why it was prescribed and check whether the indication remains valid: complicated reflux disease, Barrett's oesophagus, peptic ulcer disease, Helicobacter pylori regimen, gastroprotection in high-risk NSAID users, or antiplatelet/anticoagulant therapy with gastrointestinal risk.	Distinguish patients who may need ongoing therapy from those who may benefit from review.
Screen risk factors	Consider age >65 years, frailty, previous anaemia, osteoporosis or previous fracture, renal impairment, diabetes, poor nutritional intake, metformin, diuretics, digoxin, corticosteroids, antiplatelets, anticoagulants or chronic NSAID use.	Identify patients at higher risk of nutritional, electrolyte or bone-related complications.
Detect warning signs	Ask about fatigue, pallor, paraesthesia, cognitive changes, cramps, weakness, palpitations, syncope, seizures, recurrent falls, bone pain, gastrointestinal bleeding symptoms or unexplained weight loss.	Decide whether referral is required rather than routine advice only.
Intervene or refer	If the patient has no clear indication or is at risk, explain the issue and refer to the physician for review, possible laboratory assessment and supervised deprescribing. Provide education on correct administration and rebound symptoms.	Ensure safe, coordinated care and avoid abrupt withdrawal in unsuitable patients.

B. Active dispensing

The first dispensing encounter is essential to ensure that the patient understands the correct administration of the medicine, the importance of following the prescribed regimen and the reason for treatment. The information provided to the patient should include correct administration: the medicine should usually be taken in the morning, preferably on an empty stomach, swallowed whole without chewing or crushing, with half a glass of water. If an evening dose has been prescribed, it should be taken before dinner, also on an empty stomach.

Patients should be advised not to exceed the dose prescribed by the physician and to continue treatment only for as long as necessary. Once symptoms have resolved, they should consult a healthcare professional to assess whether treatment withdrawal is possible. They should not stop long-term treatment abruptly without prior clinical assessment, especially if there is a valid indication for continued therapy. The patient should leave the pharmacy with a clear understanding of how to take the medicine, why it has been prescribed, which symptoms require consultation and why adherence to the prescribed regimen is important.

C. Health education

Myths and misconceptions surrounding omeprazole and other PPIs contribute to indiscriminate use. Clinical guidance emphasizes that routine PPI use is not justified solely because a patient is over 65 years of age, has non-specific heartburn, or is polymedicated if the treatment regimen does not include medicines with relevant gastrolesive potential.

Health education should be implemented at the pharmacy counter, particularly when patients have questions about newly prescribed PPIs or request them as self-medication. Lifestyle and dietary measures should also be emphasized, especially when patients seek advice for dyspeptic symptoms. Patients should be informed that heartburn or reflux does not always require long-term PPI treatment. Pharmacist-recommended alternatives, such as antacids or alginates when appropriate, may be useful for occasional symptoms, provided that warning signs are absent and lifestyle measures are addressed.

Conclusions

I. PPIs are widely prescribed medicines that are effective and generally safe when the indication, dose and duration of treatment are appropriate.

II. Long-term or unjustified PPI use has been associated with vitamin B12 deficiency, iron deficiency, hypomagnesaemia and possible alterations in calcium and bone outcomes. These associations should be interpreted according to the strength of evidence for each outcome and in light of potential confounding factors.

III. Community pharmacists can contribute to safer PPI use through active dispensing, structured screening, patient education, detection of warning signs and referral for medical review when deprescribing or laboratory assessment may be appropriate.

IV. Deprescribing should be individualized, coordinated with the physician and implemented gradually when clinically appropriate, while maintaining long-term treatment in patients with a valid indication.

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Conflicts of interest

The author declares that they have no conflicts of interest.

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