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Expert Opinion Article

The Impact of Long-Term Use of Proton Pump Inhibitors (PPIs) on Drug and Vitamin Absorption in Patients

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Background

Proton Pump Inhibitors (PPIs) are among the most commonly prescribed medications worldwide for conditions related to excessive gastric acid production, such as gastroesophageal reflux disease (GERD), peptic ulcers, and Zollinger-Ellison syndrome. Their efficacy in suppressing gastric acid secretion has made them the drug of choice in both short-term and long-term management of acid-related disorders (Maideen, 2023).

Over time, concerns have been raised about the widespread and often prolonged use of PPIs, particularly when used beyond the recommended treatment duration. Chronic PPI therapy can lead to alterations in the stomach's pH environment, potentially influencing the solubility and absorption of various essential nutrients and drugs (Losurdo et al., 2023).

Vitamins such as B12, magnesium, calcium, and iron require an acidic environment for optimal absorption in the gastrointestinal tract. Long-term suppression of gastric acid by PPIs may hinder the bioavailability of these nutrients, contributing to deficiencies that can lead to serious clinical consequences, including anemia, osteoporosis, and neurological impairments (Lehault & Hughes, 2017). Furthermore, PPIs may interfere with the metabolism of co-administered drugs. This interaction could be pharmacokinetic—altering drug absorption, distribution, metabolism, or excretion—or pharmacodynamic, impacting the overall effectiveness or toxicity of the drugs taken concurrently (Koyyada, 2021).

There is growing evidence to suggest that the long-term use of PPIs may affect the absorption of cardiovascular, antifungal, antiviral, and antiretroviral drugs. This raises concerns in patients managing chronic diseases who rely on multiple medications for disease control and quality of life (Jaynes & Kumar, 2018).

Clinicians and researchers are becoming increasingly aware of the need to evaluate not only the benefits but also the potential adverse systemic effects of extended PPI therapy. Despite these concerns, PPIs continue to be available over the counter in many countries, contributing to unsupervised and prolonged use by patients (Wilhelm et al., 2013).

The elderly population is particularly vulnerable due to polypharmacy and age-related physiological changes in drug metabolism and nutrient absorption. For these patients, unnoticed vitamin deficiencies or altered drug efficacy can significantly impact health outcomes (Strand et al., 2017).

Although numerous studies have examined specific nutrient or drug interactions with PPIs, there is a lack of a comprehensive and systematic review that brings together this fragmented data to clarify the extent of the impact and the specific clinical implications (Smaoui et al., 2024).

A better understanding of these interactions is essential for guiding clinical decision-making, updating treatment guidelines, and informing

patient education about the risks of long-term PPI use (Tan & Juurlink, 2024).

Problem Statement

Despite the clinical benefits of Proton Pump Inhibitors in managing acid-related disorders, the long-term use of these medications is associated with potential adverse effects on the absorption of essential vitamins and co-administered drugs. However, a comprehensive and systematized evaluation of the nature, extent, and clinical consequences of these effects remains lacking. This gap in knowledge poses a challenge for healthcare providers in ensuring safe and effective long-term pharmacotherapy for patients on chronic PPI therapy.

Research Questions

1. What is the impact of long-term PPI use on the absorption of vitamins such as B12, calcium, magnesium, and iron in patients?
2. How does chronic PPI therapy influence the pharmacokinetics and bioavailability of other co-administered drugs?
3. What patient populations are most at risk for adverse effects related to impaired absorption due to prolonged PPI use?
4. What clinical outcomes have been associated with nutrient deficiencies or altered drug levels resulting from long-term PPI therapy?

Research Hypotheses

1. Long-term use of PPIs significantly reduces the absorption of essential vitamins such as B12, calcium, magnesium, and iron in patients.
2. Prolonged PPI therapy negatively affects the pharmacokinetics and therapeutic efficacy of certain co-administered medications.
3. Elderly patients and those with polypharmacy are more susceptible to adverse outcomes related to PPI-induced absorption impairments.

Research Aim

To systematically review and evaluate the existing literature on the impact of long-term Proton Pump Inhibitor use on the absorption of drugs and essential vitamins in patients, identifying associated clinical outcomes and vulnerable patient populations.

Research Objectives

1. To examine the evidence regarding vitamin deficiencies associated with long-term PPI use.
2. To analyze studies exploring the impact of PPIs on the absorption and metabolism of other medications.
3. To identify which patient populations are at greater risk of adverse outcomes due to prolonged PPI therapy.
4. To assess the clinical consequences of nutrient malabsorption and drug interaction caused by chronic PPI use.
5. To provide recommendations for healthcare professionals regarding the monitoring and management of patients on long-term PPI therapy.

Methodology

Research Design

This study will employ a systematic review design to comprehensively gather, evaluate, and synthesize existing research related to the impact of long-term use of Proton Pump Inhibitors (PPIs) on drug and vitamin absorption in patients. The systematic review approach allows for a transparent, reproducible, and rigorous examination of the current evidence, focusing on qualitative synthesis rather than quantitative meta-analysis. This design is appropriate to provide a broad understanding of the topic given the variability in study designs and outcomes in the available literature.

Eligibility Criteria

Studies included in this review will meet predefined inclusion and exclusion criteria to ensure relevance and quality. Eligible studies will focus on human subjects of any age who have been prescribed PPIs for a prolonged period, defined as usage exceeding three months. The review will include observational studies, randomized controlled trials, cohort studies, case-control studies, and relevant clinical trials that report on the absorption or bioavailability of vitamins (such as B12, calcium, magnesium, iron) and/or co-administered drugs affected by PPI therapy. Studies published in English within the last 20 years will be considered to capture current clinical practices and relevant findings. Articles lacking clear information on PPI duration or absorption outcomes will be excluded.

Information Sources and Search Strategy

A comprehensive literature search will be conducted across multiple electronic databases, including PubMed, Scopus, Web of Science, Embase, and Cochrane Library. The search strategy will employ relevant Medical Subject Headings (MeSH) terms and keywords such as “Proton Pump Inhibitors,” “PPIs,” “long-term use,” “drug absorption,” “vitamin absorption,” “bioavailability,” “nutrient deficiency,” and specific vitamins like “Vitamin B12,” “magnesium,” “calcium,” and “iron.” Boolean operators (AND, OR) will be used to refine searches. Additional sources, such as reference lists of selected articles and relevant systematic reviews, will be

hand-searched to identify studies not captured in the electronic search.

Study Selection
All retrieved records will be imported into a reference management software to remove duplicates. Two independent reviewers will screen the titles and abstracts for eligibility based on the inclusion criteria. Potentially relevant full texts will be obtained and assessed independently by the reviewers. Any discrepancies or disagreements will be resolved through discussion or consultation with a third reviewer to ensure unbiased selection. A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram will document the study selection process.

Data Extraction
Data from the included studies will be systematically extracted using a pre-designed data extraction form. Key information to be collected includes study characteristics (author, year, country, study design), participant demographics, duration and dosage of PPI use, types of drugs or vitamins assessed, methods used to measure absorption or bioavailability, and main findings related to nutrient or drug absorption. Two reviewers will independently extract data to minimize errors and bias, with discrepancies resolved by consensus.

Quality Assessment
The methodological quality and risk of bias of included studies will be evaluated using validated appraisal tools appropriate for the study designs, such as the Newcastle-Ottawa Scale for observational studies and the Cochrane Risk of Bias tool for randomized controlled trials. Each study will be rated on domains including selection bias, measurement bias, confounding factors, and reporting bias. This quality assessment will inform the interpretation of findings and the strength of evidence in the final synthesis.

Data Synthesis
Given the anticipated heterogeneity in study populations, PPI regimens, and outcome measures, a narrative synthesis approach will be used to summarize the findings. The synthesis will group evidence based on types of vitamins and drugs affected, study design, and patient characteristics. Patterns, consistencies, and gaps in the literature will be highlighted. The narrative will also discuss clinical implications and potential mechanisms underlying altered absorption due to long-term PPI use.

Ethical Considerations
As this research involves the analysis of previously published data and does not involve primary data collection from human subjects, ethical approval is not required. However, the review will be conducted with strict adherence to ethical guidelines for research integrity, transparency, and accurate reporting.

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