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Review Article

Inappropriate Use of Proton Pump Inhibitors (PPIs) in Elderly and Drug-Drug Interaction: A Narrative Review

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Abstract

Background: PPIs are highly effective for treating gastrointestinal disorders, including dyspepsia, peptic ulcer disease, gastritis, and gastroesophageal reflux disease (GERD). Furthermore, for the prophylaxis of NSAIDs and to mitigate gastrointestinal bleeding in patients receiving glucocorticoids, antiplatelet agents, or anticoagulants, particularly in the elderly population. The prescribing of PPIs among elderly patients remains a widespread issue that can lead to inappropriate use, hospital admission, or discharge. Additionally, the inappropriate use of PPIs can lead to possible drug-drug interactions.
Objective: This narrative review aims to comprehensively assess inappropriateness associated with PPIs use in the elderly population and drug-drug interactions.
Methods: Studies published from 2014 to 2024 were identified through a comprehensive search of multiple databases, including PubMed, Google Scholar, and ScienceDirect.
Results: Long-term dangers such as infections and nutritional deficits are increased by inappropriate usage, which is defined by unwarranted commencement and lengthy duration. Simultaneously, PPIs present significant DDI hazards through modulating the absorption of pH-dependent medications and blocking cytochrome P450 enzymes, particularly CYP2C19. These risks are made worse by the prevalence of polypharmacy and aging-related deterioration of renal and hepatic function.
Conclusion: In clinical practice, these findings call for systematic drug reviews and organized deprescribing programs to detect and manage high-risk combos. Implementing PPI stewardship programs in hospital and community settings is highly advised at the policy and systems level to enhance pharmaceutical safety in this susceptible population and to encourage evidence-based, guideline-concordant prescription.

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INTRODUCTION

Proton pump inhibitors (PPIs) are group of medications widely prescribed for gastrointestinal disorders.[1,2] PPIs are highly effective for treating gastrointestinal disorders in elderly populations, including dyspepsia, peptic ulcer disease, gastritis, and gastroesophageal reflux disease (GERD).[3] There were 7.238 as new users, and 4.942 were newly consistent users. The highest incidence of new PPIs use was observed among patients discharged from gastroenterology (32,2%), hematology (31,8%), oncology (29,2%), and the highest persistent usage was reported in elderly patients discharged.[4] PPIs frequently prescribed for the prophylaxis of NSAID and to mitigate gastrointestinal bleeding in patients receiving glucocorticoids, antiplatelet agents, or anticoagulants.[5] This is because elderly experience many complications of disease and require a lot of therapy. Therefore, inappropriate PPIs use has highly occurred. Older adults often present with multiple coexisting conditions, including cardiovascular, metabolic, degenerative joint, and digestive disorders, which contribute to increased frailty.[6] This review explores the consequences of polypharmacy in this population, adressing age-related physiological changes in drug metabolism and the dangers of excessive medication. Particular emphasis is placed on proton pump inhibitors (PPIs), a widely used class of medications that offer important therapeutic benefits but also carry risks if inappropriately prescribed. Given how aging affects drug absorption and processing, prescriptions for older patients require careful assessment.

A notable gap exists in the literature, as there remains a paucity of comprehensive narrative reviews that simultaneously address the dual challenges of inappropriate PPI prescribing and clinically significant drug-drug

interactions within the vulnerable geriatric population. The recent narrative review on PPI use in older patients highlights risks and deprescribing strategies,[7] but does not address clinically relevant drug interactions as a central theme alongside inappropriate use, underscoring the need for more holistic narrative syntheses in this field. The physiological changes associated with aging impact how the body absorbs and processes medications, underscoring the critical need for meticulous prescription review. The probability and severity of these harms, which encompass nutrient deficiencies, infections, alignant diseases, and pharmacokinetic interactions, are positively associated with the length of PPI exposure, patient age, and comorbid disease burden.[8]

Inappropriate prescribing of PPIs among elderly patients remains a widespread issue. Inappropriate PPI use was identified in 51.92% upon hospital admission, increasing to 57.25% at discharge. Age over 65 at discharge (OR = 0.023, 95% CI = 0.002–0.281, p = 0.003) was found to be protective factors against potentially inappropriate PPI use.[9] Similarly, in British Columbia, Canada, between 2000 and 2018, the prevalence of PPI use is high among the elderly population in British Columbia, Canada. The frequent use of PPIs is more effective, resulting from a desire to reevaluate the need for continued treatment.[10] The inappropriate use of PPIs can lead to possible drug interactions.

PPIs influence drug interactions through several mechanisms, such as enhancing the absorption of weakly acidic drugs like aspirin. However, the effects of PPIs on the H+/K+ ATPase enzyme remain largely unknown. Directly or indirectly, PPIs may be involved in various physiological processes, including interactions with specific brain enzymes (potentially increasing dementia risk), pancreatic secretion (affecting blood glucose levels), bone health (increasing fracture risk), kidney function, sperm motility, and viral replication.[11–13] Omeprazole and lansoprazole are effective inhibitors of cytochrome P450 isoenzymes, particularly CYP2C19 and CYP2D6. In vitro studies demonstrate that omeprazole and lansoprazole inhibit CYP2C19, CYP3A4, CYP2C9, and CYP2D6, increasing the risk of toxicity in co-administered drugs. Although PPI co-prescription is common, most interactions do not result in clinically significant issues.[14] Therefore, PPIs should be administered with appropriate warnings and objectives to avoid inappropriate use and increased risk of side effects.[15] The use of PPIs in elderly populations is widespread, serving both as a therapeutic intervention for specific gastrointestinal disorders and as a preventive measure against medication-induced gastrointestinal complications. In this narrative review, the inappropriateness of PPI usage in the elderly population and mild to severe drug-drug interactions in both inpatient and outpatient settings will be thoroughly evaluated.

RESEARCH METHODS

Study Selection

The study was conducted as a narrative literature review. Relevant studies published between 2014 and 2024 were identified through a comprehensive search of multiple electronic databases, including PubMed https://pubmed.ncbi.nlm.nih.gov, Google Scholar https://scholar.google.com, and ScienceDirect https://www.sciencedirect.com. The search strategy employed combinations of Medical Subject Headings (MeSH) and free-text terms using Boolean operators AND and OR. The primary search terms included: *"Proton Pump Inhibitors" OR "Omeprazole" OR "Lansoprazole" OR "Esomeprazole" OR "Pantoprazole" OR "Rabeprazole"*, combined with *"Inappropriate Use" OR "Potentially Inappropriate Prescribing"*, and *"Drug Interaction"*, as well as *"Elderly" OR "Older Adults"*. For PubMed searches, relevant MeSH terms such as *"Proton Pump Inhibitors"*, *"Drug Interactions"*, and *"Aged"* were applied when available. Additional studies were identified by manual screening the reference lists of relevant articles. The article selection process followed a two-stage screening. Initially, titles and abstracts were screened for relevance based on inclusion criteria. Subsequently, the full texts of potentially eligible articles were assessed. Inclusion criteria prioritized original research articles (experimental and observational study) published in English that specifically investigated either PPI prescribing in elderly populations or clinically significant drug-drug interactions involving PPIs. Studies falling outside the defined scope, timeframe, or language were excluded.

Data Synthesis

Data extraction was guided by the review's primary objectives to evaluate the nature of inappropriate PPI use in the elderly and to analyze associated drug-drug interactions. Information pertinent to these themes, such as study design, population characteristics, mechanisms of identified interactions, and key findings were systematically extracted from the selected literature. The findings were then narratively synthesized to provide a comprehensive analysis of the current evidence, identify common patterns, and highlight knowledge gaps in the field.

RESULT AND DISCUSSIONS

Inappropriate Use of PPIs in Elderly

The study revealed that 61.9% of patients were prescribed medications for peptic ulcer disease or GERD at discharge, with PPIs accounting for 96% of these prescriptions. Despite this high prevalence, only 54.4% of prescriptions aligned with clinical indications, highlighting significant rates of inappropriate use. Pantoprazole was the most frequently prescribed PPI (27.9%). The large and inappropriate use of gastric ulcer and GERD medications in acutely hospitalized elderly from 2010 to 2016. Hospitalization failed to improve the quality of medication prescribing in this high-risk and frail population, by showing a decrease in the appropriateness of using or not using the drug for gastric ulcers and GERD.[16] The study was evaluated PPI prescription appropriateness based on Italian Medicines Agency (AIFA) guidelines. Overprescribing, defined as prescribing without AIFA-recognized indications, was observed in 30% of patients at discharge, while underprescribing, defined as not prescribing despite clinical indications, occurred in 11%. Overprescribing was negatively associated with age (OR = 0.88, 95% CI: 0.85–0.91), depression (OR = 0.58, 95% CI: 0.35–0.96), aspirin use (OR = 0.03, 95% CI: 0.02–0.06), and systemic corticosteroids (OR = 0.02, 95% CI: 0.01–0.04). Underprescribing was positively linked to advanced age (OR = 1.09, 95% CI: 1.04–1.14), aspirin use (OR = 24.0, 95% CI: 11.5–49.8), systemic corticosteroids (OR = 19.3, 95% CI: 11.5–49.8), and comorbidities (OR = 1.22, 95% CI: 1.04–1.42).[17]

Inappropriate PPI use was identified in 82.5% of elderly patients receiving long-term care, with no explicit indication for their use. PPIs in the elderly are quite common, and only a few PPI prescriptions include the indication in the patient's electronic record. Additionally, the lansoprazole prescription was ongoing with no authorization or reevaluation date.[18] Among PPI users, half reported gastrointestinal symptoms regardless of PPI therapy, while 17.2% (n = 21) were prescribed PPIs for indications other than gastroprotection, despite their need for such therapy. Although elderly patients often require PPI treatment, evidence suggests that low-dose regimens or on-demand use may serve as effective strategies to minimize unnecessary high-dose PPI prescriptions.[19] Long-term PPI use should be reassessed at least annually, and discontinuation should be considered in the absence of clear indications. Patient education regarding the risks and benefits of PPIs, along with regular monitoring, is essential to minimize adverse effects and ensure appropriate prescribing practices.[10] A study in Jordan highlighted the low level of knowledge among elderly patients regarding inappropriate long-term PPI use, underscoring the need for comprehensive evaluations to mitigate potential adverse effects.[20]

Interventions aimed at deprescribing PPIs in elderly patients have shown promising results. A Canadian study conducted in residential care facilities with a mean patient age of 80 ± 11.8 years targeted deprescribing among long-term users of pantoprazole (40 mg/day; 93%) and esomeprazole (40 mg/day; 78%) after at least six months of therapy. Eight weeks following discontinuation, 70% of participants experienced no significant symptoms.[21] Similarly, a prospective study with a mean patient age of 84.3 ± 9.9 years deprescribed PPIs in 80% of patients using tapering or discontinuation protocols based on clinical status. After three months, 82% of patients remained symptom-free.[22] In hospital settings, the OPERAM (Optimizing Therapy to Prevent Avoidable Hospital Admissions in Multimorbid Older Adults) study in Europe demonstrated that deprescribing occurred in one out of five patients upon admission and was twice as likely during hospitalization.[23] In Toronto, the Acute Care for the Elderly (ACE) unit reported a higher deprescribing rate of 31% among survivors, attributed to the unit's multidisciplinary, geriatric-focused approach prioritizing medication safety.[24]

Several important clinical implications for optimizing PPI use in the elderly are presented by the findings. The first is that organized drug reviews should be implemented during care transitions, such hospital admission and discharge, to specifically reevaluate the continued need for PPI therapy due to the high rate of improper prescriptions. Second, the success of deprescribing therapies, which showed that most patients did not have any symptoms upon withdrawal or dose reduction, encourages the use of regulated tapering protocols instead of abrupt termination. For example, step down to a lower dose or an H2-receptor antagonist.[19] Third, physicians ought to make it mandatory for each PPI prescription to include a precise and legitimate indication that can be audited on a regular basis in order to address the widespread deficiency of recorded indications. Lastly, because some medications (such as corticosteroids or aspirin) have been linked to incorrect prescribing practices,[17] care should be taken to deprescribe opportunities for individuals taking these medications who do not have any other risk factors for gastrointestinal issues. These feasible steps are crucial for bringing PPI use into compliance with evidence-based recommendations for geriatric care, especially when accompanied by patient education of possible risks. All the results can be seen in **Table 1**.

Table 1. Inappropriate Use of PPIs in Elderly Population

Design Study	Years	Samples	Results	References
A multicenter, cross-sectional	2008, 2010, 2012, 2014, and 2016	Age 65 or older, users at discharge (n=2412) and at admission (n=1954)	2412 (61.9%, 95% CI: 60.3-63.4%) patients were prescribed with drugs at hospital discharge. Among 1444 (=2412-968) patients inappropriately prescribed, 162 (11.2%) aged 65-74 years were prescribed NSAIDs or ASA but did not present additional risk factors for gastrointestinal bleeding.	[25]
A multicenter prospective observational	Between June 2010 and May 2011	Age > 65 years, 1081 patients discharged from hospital	Underprescribing (OR=1.21, 95%CI=1.09-1.33) and overprescribing (OR=0.88, 95%CI=0.85-0.91)	[26]
Retrospective cohort study	Between January 2018 and January 2022	Age 65 years or older during hospital stay	Lansoprazole durations (mean=314.4 days±306.5). The minimum treatment was 3 days, and the maximum was 1198 days.	[27]
Cross-sectional	June 2019 to December 2020	Age 65 years or older, 388 older adults participated	Deprescribing (n=216, 55.7%) with 33.5% one medicine, 18.8% two medicines, and 3.4% three medicines. Inappropriate long use of PPI (26.2%) and inappropriate dose 16.4%	[28]
Cross-sectional	During January 2020	Older adults (≥ 55 years old)	Participants had never tried reducing (87.5%) or stopping (89.5%) PPI use	[29]
Prospective, nonblinded, uncontrolled, pre-post quality. improvement	December 2021 to April 2022	Age 84.3±9.9	Eligible (71%) and not eligible (29%) for deprescribing	[22]
Prospective, longitudinal cohort study	2016-2018	Adults aged 70 years and older, 1879 patients	496 (45.9%) potentially inappropriate indication at admission. At discharge, 133 (24.9%) of 534 patients in intervention group and 92 (16.8%) of 546 patients in control group had deprescribing.	[23]
Retrospective cohort study	September 2017 to December 2017	65 years or older	8 (9%) of 93 patients was inappropriate indication and 25 (27%) was unclear indication of PPI use	[24]

Drug-Drug Interactions of PPIs

The results of drug interactions can be seen in **Table 2**. Age-related pharmacokinetic and pharmacodynamic alterations in elderly may significantly increase the clinical impact of drug-drug interactions. Even in the absence of obvious kidney disease, aging in linked to a steady decline in renal function, decrease hepatic flow, and activity of specific cytochrome P450 enzymes.[30] Genetic variation in the CYP2C19 enzyme affects the response to proton pump inhibitors (PPIs), with individuals categorized by genotype into poor metabolizers (PM), intermediate metabolizers (IM), normal metabolizers (NM), rapid metabolizers (RM), and ultra-rapid metabolizers (UM). PMs, characterized by two non-functional alleles such as CYP2C19*2/*2 or CYP2C19*3/*3, exhibit slow metabolism, resulting in plasma PPI levels that are two to three times higher than those observed in NMs, who carry two normal alleles (CYP2C19*1/*1), and typically respond well to standard doses. Intermediate metabolizers (CYP2C191/*2 or *1/3) generally tolerate standard dosing, although dose adjustment may be required in elderly patients with comorbid liver disease or extensive polypharmacy IMs, with one normal allele and one non-functional allele (CYP2C19*1/*2 or CYP2C19*1/*3), experience slower metabolism than NMs, with standard doses generally being practical, although dose adjustments may occasionally be necessary. RMs carrying one normal allele and one increased-function allele (CYP2C19*1/*17) may require dose increases of 50–100% to achieve optimal acid suppression. In contrast, UMs, who possess two increased-function alleles (CYP2C19*17/*17), often require doses up to twice the standard amount or the use of PPIs that are not metabolized by CYP2C19, such as rabeprazole, to achieve adequate therapeutic effects. Dose adjustments based on CYP2C19 genotyping are essential to optimize efficacy and minimize the risk of adverse effects.[31–33]

These identical isoforms are also responsible for the metabolism of other drugs. Omeprazole, for example, has been reported to inhibit the metabolism of drugs such as diazepam,[34] phenytoin,[35] and clarithromycin.[36] Omeprazole reduces the systemic clearance of diazepam by 30% and phenytoin by 10%, potentially increasing their plasma concentrations and enhancing pharmacologic effects.[28] Clopidogrel is a prodrug that requires conversion to its active metabolite, which inhibits platelet aggregation by irreversibly binding to the P2Y12 adenosine diphosphate receptor on platelets. Specific cytochrome P450 isoenzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP3A4, are involved in the biotransformation of clopidogrel, with CYP2C19 and CYP3A4 playing the most significant roles. PPIs act as competitive inhibitors of CYP2C19, the primary isoenzyme required for clopidogrel activation. Co-administration of

omeprazole significantly reduces the effectiveness of clopidogrel by impairing its conversion to the active metabolite.[37] Based on this, drug interactions involving omeprazole have been widely reported, although not all of these interactions are considered clinically significant.

Table 2. Common Drug Interactions with Moderate to Severe Risk

PPIs	Drug Interaction	Mechanism	Results	References
Omeprazole/ Esomeprazole/Lansoprazole	Clopidogrel	Inhibition of clopidogrel metabolism of CYP3A4 and CYP2C19 to its active metabolite	Reduces the antiplatelet effect of clopidogrel	[25]
Pantoprazole/ Rabeprazole		Does not affect the pharmacokinetics and efficacy of clopidogel	-	
Lansoprazole/Omeprazole/ Esomeprazole	Rifampicin	Strong CYP2C19 induction by rifampicin may decrease the serum concentration of PPIs	Decreases the effectiveness of PPIs	[26]
Omeprazole/ Pantoprazole	Itraconazole/Ketoconazole	It may decrease of AUC_{0-24} and Cmax of itraconazole by increasing gatric pH	Reduces the efficacy of itraconazole	[27]
Omeprazole	Carbamazepine	Carbamazepine-mediated induction of CYP3A4 for reduction of omeprazole	Decreases the effectiveness of omeprazole	[28]
Omeprazole/ Esomeprazole	Phenytoin	May increase the serum concentration of phenytoin by affecting hepatic enzyme CYP2C9	Increases the serum concentration and effect of phenytoin	[29]

The concurrent use of methotrexate (particularly at high doses) with omeprazole, esomeprazole, and pantoprazole has been shown to reduce methotrexate clearance, leading to elevated serum levels of methotrexate and its metabolite, 7-hydroxy methotrexate. This may result in methotrexate toxicity.[38] A case of severe myalgia was reported following a methotrexate injection of 15 mg in a lymphoma patient taking pantoprazole at a dose of 20 mg/day. The total drug exposure (AUC144) for 7-hydroxymethotrexate was nearly 70% higher when pantoprazole was co-administered compared to administration without pantoprazole. The drug's half-life doubled, suggesting an interaction that affects renal elimination rather than metabolism.[39]

Proton pump inhibitors (PPIs) may reduce the effectiveness of anticancer therapies, such as tyrosine kinase inhibitors (TKIs), cyclin-dependent kinase (CDK) 4/6 inhibitors, and immune checkpoint inhibitors (ICIs). This occurs through mechanisms such as reducing gastric acid secretion, impairing drug absorption, modifying the gut microbiome, and modulating the response to ICIs. Alterations in the gut microbiome caused by PPI use have been associated with reduced ICI efficacy.[40] A study demonstrated a 16% increased risk of mortality among cancer patients treated with TKIs, suggesting that PPIs may reduce TKI absorption. Notably, nearly 1 in 4 older cancer patients receiving TKI therapy also concurrently use PPIs, and this combination has been associated with a higher risk of mortality. For example, a 21% increased risk of death was observed in lung cancer patients receiving erlotinib concurrently with PPIs.[41] Among all TKIs, erlotinib exhibits the strongest potential for drug-drug interactions (DDIs).[42]

Drugs with high affinity for CYP3A4, such as ketoconazole or fluconazole, can influence the bioavailability of PPIs by increasing omeprazole concentrations.[43] For instance, a daily dose of 100–200 mg of ketoconazole for four days was shown to inhibit the formation of omeprazole sulfone in all patients, leading to a two-fold increase in serum omeprazole concentrations in poor metabolizers.[44,45] Additionally, PPIs are at risk of interacting with other medications commonly used for gastric conditions. Sucralfate, one of the frequently co-administered drugs, is a basic aluminum salt of sucrose octasulfate[46], which stimulates the release of bicarbonate ions, enhances mucus secretion, and exerts a buffering effect on the gastric mucosa. As a result, the protonation and conversion of PPIs into their active forms are reduced, subsequently decreasing their effectiveness.[47]

Clinically, PPI interactions with other medications can have detrimental effects that call for extra care while treating older patients. Particularly in individuals with cardiovascular comorbidities, interactions with omeprazole and esomeprazole can decrease the antiplatelet efficacy of clopidogrel, raising the risk of recurrent cardiovascular events such myocardial infarction and stroke. The activation of CYP450 enzymes during interactions with rifampin and carbamazepine, on the other hand, can lower serum PPI levels, resulting in insufficient acid control and possibly causing a recurrence of GERD symptoms or problems from peptic ulcers. Treatment failure for systemic fungal infections may come from interactions with azole antifungals, such as itraconazole, which reduce therapeutic efficacy because of poor absorption. Neurological symptoms including ataxia, nystagmus, or severe drowsiness can result from interactions with phenytoin, which actually raise serum levels and the risk of intoxication. These consequences highlight how important it is to carefully examine medications, choose safer PPIs, adjust dose time, and closely monitor therapeutic response

and adverse effects in older patients who are at risk due to polypharmacy and altered pharmacokinetics. This study did not use a randomized controlled trials (RCTs) design to assess inappropriate use of PPIs in the elderly due to the limited results of research using RCTs. In addition, the researchers did not include extensive drug interactions between PPIs and other drugs because the researchers only wanted to emphasize cases of moderate to severe drug interactions that are likely to occur frequently in clinical settings.

A standardized evaluation of the risk of bias for the primary studies that were included was outside the purview of this analysis due to its narrative nature. Because of this, even while the review summarizes the main conclusions and topics, the strength of the evidence varies depending on the methodological advantages and disadvantages of each source.

CONCLUSION

The evidence on the two main issues with the use of proton pump inhibitors (PPIs) in the elderly—inappropriate prescription practices and clinically significant drug-drug interactions (DDIs)—is summarized in this narrative review. Long-term dangers such as infections and nutritional deficits are increased by inappropriate usage, which is defined by unwarranted commencement and lengthy duration. Simultaneously, PPIs present significant DDI hazards through modulating the absorption of pH-dependent medications and blocking cytochrome P450 enzymes, particularly CYP2C19. These risks are made worse by the prevalence of polypharmacy and aging-related deterioration of renal and hepatic function. In clinical practice, these findings call for systematic drug reviews and organized deprescribing programs to detect and manage high-risk combos. Implementing PPI stewardship programs in hospital and community settings is highly advised at the policy and systems level to enhance pharmaceutical safety in this susceptible population and to encourage evidence-based, guideline-concordant prescription.

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AUTHOR CONTRIBUTION STATEMENT

Thendi Abdul Arief: Conceptualization, Methodology, Data collection, Data analysis, Writing – original draft preparation, Writing – review and editing; **Nabila Risti Rachmadi**: Methodology, Data collection, Data analysis, Writing – original draft preparation, Writing – review and editing; **Hanum Hasifah Fahriah**: Methodology, Data collection, Data analysis, Writing – original draft preparation, Writing – review and editing; **Agung Endro Nugroho**: Conceptualization, Supervision.

CONFLICT OF INTEREST

All authors declare that there is no potential conflict of interest with the research, authorship, and/or publication of this article.

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