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Adverse outcomes of inappropriate proton pump inhibitor use in geriatric populations – a review

Negatywne skutki niewłaściwego stosowania inhibitorów pompy protonowej w populacji geriatrycznej – przegląd

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Abstract

Introduction. *We examine the widespread use of Proton Pump Inhibitors (PPIs) in the elderly, focusing on inappropriate prescribing.* **Aim.** *Our aim is to highlight the need for reconsidering PPI prescribing in elderly people due to potential adverse effects.* **Materials and Methods.** *An extensive review of existing literature and clinical data on PPI use in older patients. We analyze studies and case reports to ascertain the risks and benefits of PPIs in this the elderly demographic.* **Results.** *Our findings point to a significant trend of PPI overprescription in elderly patients, with an accompanying increase in health risks, from mild discomfort to severe complications. The data establishes a clear connection between extended inappropriate PPI use and elevated health risks in the elderly.* **Conclusion.** *We advocate for a more cautious approach to prescribing PPIs in older adults. There exists a need for regular monitoring and reassessment of PPI therapy. We suggest deprescription as a viable strategy to mitigate the risks of adverse outcomes, underscoring the importance of individualized, evidence-based medication management for elderly people. (Gerontol Pol 2024; 32; 41-48) doi: 10.53139/GP.20243206*

Keywords: *PPI overprescription in the elderly, adverse effects of PPIs, PPI deprescribing, PPIs and dementia risk, PPI use and musculoskeletal system.*

Streszczenie

Wstęp. *W prezentowanym przeglądzie badamy powszechne stosowanie Inhibitorów Pompy Protonowej (PPI) u osób starszych, skupiając się na równowadze pomiędzy korzyściami i ryzykiem.* **Cel.** *Celem naszej pracy jest podkreślenie potrzeby regularnej oceny zasadności przepisywania PPI w populacji geriatrycznej ze względu na potencjalne działania niepożądane.* **Materiał i metody.** *Przegląd literatury i danych klinicznych odnośnie użycia PPI u osób starszych. Przeanalizowaliśmy badania i opisy przypadków, aby ustalić ryzyko i korzyści wynikające z ich przepisywania w tej grupie pacjentów.* **Wyniki.** *Nasze obserwacje wskazują na znaczący trend nadmiernego przepisywania PPI u starszych pacjentów, co wiąże się ze wzrostem ryzyka działań niepożądanych - od lekkiego dyskomfortu do poważnych komplikacji. Dane wykazują związek pomiędzy przewlekłym stosowaniem PPI, a podwyższonym ryzykiem działań niepożądanych.* **Wnioski.** *Przeprowadzona przez nas analiza wskazuje na konieczność wyważonego podejścia przy przepisywaniu PPI osobom starszym. Pragniemy zwrócić uwagę na potrzebę regularnego monitorowania i oceny aktualnych wskazań do terapii. Chcielibyśmy również podkreślić konieczność stosowania indywidualnego podejścia do pacjenta i odstawianie PPI przy braku wskazań do ich stosowania. (Gerontol Pol 2024; 32; 41-48) doi: 10.53139/GP.20243206*

Słowa kluczowe: *niewłaściwe przepisywanie IPP u osób starszych, działania nieporządane IPP, odstawianie IPP, IPP i ryzyko demencji, IPP i układ mięśniowo-szkieletowy.*

Introduction

Proton pump inhibitors (PPIs) were first brought to the market nearly 30 years ago with a specific purpose: to treat acid-related conditions such as peptic ulcer disease and gastroesophageal reflux disease (GERD). The remarkable efficacy of PPIs in suppressing gastric acid secretion led to their widespread adoption and use.

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However, over time, the use of PPIs has expanded beyond their initial indications. This may partly be due to their perceived safety profile and the lack of satisfactory alternatives for conditions involving gastric acid overproduction. This has resulted in PPIs being among the top prescribed drugs in the United States, with the National Center for Health Statistics reporting in 2018 that they were the third most commonly prescribed drug class in the United States [1]. At that time, it was estimated that approximately 15.3 million adults were using PPIs.

Unfortunately, this rise in the usage of PPIs is increasingly associated with concerns of potential overuse and misuse. An observational study conducted in the Netherlands, which included around 150,000 patients, found that over half of individuals prescribed PPIs in primary care had no suitable indication for use [2].

Inappropriate use of PPIs raises serious concerns, especially in the context of the geriatric population. Geriatric patients are particularly vulnerable due to multimorbidity and the high likelihood of polypharmacy. Polypharmacy can contribute to a decline in mental and physical functions in elderly patients [3]. PPIs are potentially inappropriate medications for this age group due to their association with several side effects and adverse events.

In our literature review, we analyze the issue of PPI overprescription in the context of the geriatric population that affects patient morbidity and increased hospitalization.

Aim

Our aim is to highlight the need for reconsidering PPI prescribing in elderly people due to potential adverse effects.

Materials and Methods

Our literature review was conducted using a systematic approach with predefined criteria to ensure comprehensive analysis. We searched the PubMed database using search parameters that were limited to articles published between 2017 and 2023.

We used the following keywords: ‘proton pump inhibitors’, ‘PPIs’, ‘geriatric population’, ‘misuse’, and ‘PPI deprescribing’.

The inclusion criteria for this review were studies written in English that explored the misuse and over-prescription of PPIs within the geriatric population. Studies that focused solely on other age groups, did not discuss PPI misuse or over-prescription, or were not in English were excluded from this review.

Results

Proton pump inhibitors (PPIs) are widely prescribed due to their efficacy in managing acid-related disorders. However, their safety profile in the geriatric population necessitates closer scrutiny due to age-associated physiological changes that can exacerbate side effects.

Short-term adverse reactions to proton pump inhibitors (PPIs) in older adults range in a spectrum of symptoms from mild discomfort to more debilitating conditions. Headaches, for instance, are experienced by approximately 1-3% of PPI users and can lead to, for example, increased use of analgesics, raising concerns for polypharmacy. Gastrointestinal side effects of PPI use such as nausea, which affects roughly 1-5% of patients, constipation, affecting 1-5% of PPI users, and diarrhea and abdominal pain, 2-5% and 1-5% of individuals respectively, can exacerbate pre-existing conditions common in older adults. These include decreased appetite, weight loss, nutritional deficiency, decreased mobility and increased reliance on antidiarrheal drugs and also laxatives in the elderly, complicating their already complex medication regimens. Flatulence, reported by 1-3% of patients on PPI therapy may lead to social withdrawal and isolation. Rashes, occurring in about 1-2% of those taking PPIs may lead to compromised skin integrity, increasing the risk or bed sores and lead to significant discomfort and an increased risk of secondary infections. Dizziness, reported by 1-3% of PPI users can result in falls, fractures, and a cascade of health complications. Similarly, muscle pain, though experienced by only 1-2% of individuals on PPIs, can exacerbate pre-existing musculoskeletal issues, diminish functional independence, and erode quality of life.

The long-term use of proton pump inhibitors (PPIs) in the geriatric cohort presents a multifaceted challenge, with implications that extend to bone health, susceptibility to infections, drug interactions, nutritional status, renal function, and cognitive health.

Osteoporotic fractures are a significant concern, with PPIs potentially impairing calcium absorption, a mineral vital for bone integrity. This effect can exacerbate the already increased risk of fractures in the elderly, leading to mobility issues and a diminished quality of life. Infections pose a heightened risk due to the reduction in gastric acid, a natural barrier to pathogens. Pneumonia and Clostridium difficile, in particular, can be life-threatening in this population, and the use of PPIs may increase susceptibility to these conditions. Polypharmacy is common in the elderly, and PPIs can complicate this issue

through drug-drug interactions. These interactions may reduce the effectiveness of other medications, especially those that require an acidic environment for absorption, potentially leading to suboptimal treatment outcomes. Nutritional deficiencies are another significant consequence of long-term PPI use. Deficiencies in vitamin B12, magnesium, and calcium can lead to an array of health issues, including anemia, neuromuscular symptoms, and further bone density loss. Emerging evidence suggests a potential link between chronic PPI use and kidney injury. Given the pre-existing vulnerability of renal function in older adults, this association is particularly concerning and warrants careful monitoring. Moreover, there is a growing body of research exploring the potential connection between long-term PPI use and cognitive decline, including an increased susceptibility to dementia. While the evidence is not yet conclusive, the possibility of such a link adds another layer of complexity to the risk-benefit analysis of PPI therapy in the elderly.

The findings highlighted by Holmfridur Helgadottir and Einar S. Bjornsson [4] in their systematic review shed light on an important aspect of proton pump inhibitor (PPI) management. The potential for a significant proportion of patients to either discontinue or reduce their long-term PPI therapy suggests that these medications might be overprescribed or continued for longer than necessary in many cases.

The fact that approximately 30% of patients could cease using PPIs, and up to 80% could lower their dosage, indicates that regular reassessment of the need for ongoing PPI therapy could be beneficial. This approach aligns with the principles of deprescribing, which involves the systematic process of identifying and discontinuing drugs in instances where existing or potential harms outweigh the benefits within the context of an individual patient's care goals, current level of functioning, life expectancy, values, and preferences.

Impact of PPIs on the Musculoskeletal System in Geriatric Patients

The influence of PPIs on the musculoskeletal system, particularly in the geriatric demographic, has been the subject of numerous studies, with a focus on bone health and fracture risk [5]. Longitudinal studies have illuminated a correlation between extended PPI therapy and an elevated risk of fractures, especially of the hip, which could be attributed to diminished calcium absorption or alterations in bone metabolism. A pivotal study employing a propensity-score matched cohort methodology contrasted the incidence of fractures over a five-year span between new users of PPIs and those initiating treatment with histamine 2 receptor antagonists (H2RAs) [6]. This investigation not only highlighted a surge in PPI utilization over the preceding two decades but also unveiled an association with a heightened risk of hip fractures when contrasted with the commencement of H2RAs. The implications of these findings are particularly significant for older adults, who are already at an increased risk for osteoporosis and related fractures.

The potential for PPIs to interfere with calcium homeostasis—either through diminished absorption in the gut or through more complex metabolic pathways—necessitates a careful re-evaluation of the risks and benefits of long-term PPI use in this vulnerable population [7]. Clinicians are urged to consider alternative therapies or the lowest effective PPI doses for the shortest duration necessary, particularly in those with pre-existing risk factors for bone loss or fractures. Additionally, the research underscores the need for ongoing monitoring of bone health in elderly patients prescribed PPIs, including periodic bone density assessments and proactive measures to mitigate fracture risk.

Additional research further corroborates the link between excessive PPI use and orthopedic complications [8]. A comparative analysis of the five-year knee replacement risk among patients initiating therapy with various PPIs (omeprazole, pantoprazole, lansoprazole, rabeprazole, or esomeprazole) against those initiating H2RAs revealed an elevated risk associated with the PPI cohort. Intriguingly, this elevated risk was not observed in initiators of lansoprazole, rabeprazole, or esomeprazole.

The propensity for falls among the elderly treated with PPIs is a pressing concern, given their potentially catastrophic outcomes. Observational research has drawn a connection between extended use of proton pump inhibitors (PPIs) and a rise in the occurrence of falls [9]. This association suggests that the influence of PPIs on the musculoskeletal system may extend beyond the direct implications on bone health. The increased risk of falls could stem from various PPI-induced factors, such as electrolyte imbalances, particularly hypomagnesemia, which can lead to muscle weakness, or from PPI-related dizziness and neurological effects that could compromise gait and balance. Moreover, the potential for PPIs to exacerbate osteoporosis and reduce bone strength may also increase the severity of injuries sustained during falls.

Proton Pump Inhibitors and Renal Function in the Elderly

Hart et al.'s 2019 retrospective cohort study examined the nephrotoxic implications of proton pump inhibitors (PPIs) among older adults [10]. The analysis was based

on 192,936 individuals and suggests a correlation between PPI consumption and an elevated occurrence of both acute and chronic kidney disease. This correlation was most accentuated among individuals aged 65 and above. Kidney disease, especially in the elderly, is often associated with increased morbidity, mortality, and decreased overall quality of life. The kidneys' natural decline in function with age makes the elderly more susceptible to drug-induced nephrotoxicity.

This finding aligns with earlier research by Lazarus et al. where an association between PPI use and the risk of chronic kidney disease was described [11]. Researchers discovered that the use of PPIs was independently linked to increased (between 20% and 50%) likelihood of developing incident CKD. Comparable results were illustrated for the occurrence of AKI. The risk was exclusive to PPI medications, as the independent association with chronic kidney disease was not observed with the use of H2 receptor antagonists, prescribed for the same indications as PPIs.

Furthermore, Xie et al., also identified a correlation between PPI exposure and an elevated risk of developing CKD, advancing kidney disease, and the likelihood of progression to the end stage renal disease [12]. The findings further indicate a proportional relationship between the duration of exposure and the risk of renal outcomes. Finally, Arora et al. (2016) also found that PPIs are associated with an increased risk of developing chronic kidney disease in adults [13].

Moreover, Liu et al. concluded that the use of IPP has also been shown to increase the risk of kidney stones [14]. The duration of PPI usage displayed a dose-response correlation with kidney stones. Additionally, a correlation was observed between prolonged PPI usage and the recurrence of kidney stones in individuals with a history of such stones, highlighting a significant linear relationship.

Proton pump inhibitor use and bacterial infections

Proton pump inhibitors (PPIs) are commonly utilized for the management of acid-related disorders. Despite their efficacy, concerns regarding their safety profile have emerged, especially in the context of bacterial infections.

Small intestinal bacterial overgrowth (SIBO) is a notable complication, with studies including a meta-analysis by Lo and Chan substantiating the association between PPI usage and an elevated risk of SIBO [15,16]. This link was predominantly evident when SIBO was diagnosed through duodenal or jejunal aspirate culture. The hypothesized mechanism involves the suppression of gastric acid secretion, a critical barrier to bacterial overgrowth, and potential alterations in intestinal motility.

Clostridium difficile infection (CDI) represents another significant concern [17]. Janarthanan et al. conducted a meta-analysis indicating an increased incidence of CDI in patients on PPI therapy. This finding is of particular relevance to the elderly, who may experience more severe complications from CDI, such as dehydration and sepsis. The presumed pathophysiological pathway involves diminished gastric acid production, leading to impaired spore inactivation and alterations in gut microbiota, compromising resistance against C. difficile colonization.

Furthermore, the relationship between PPI use and community-acquired pneumonia (CAP) has been explored. Lambert et al. (2015) and Laheij et al. (2004) provided evidence suggesting an elevated risk of CAP in outpatient settings among PPI users [18,19]. The mechanism, although not fully elucidated, might involve changes in the upper gastrointestinal tract's microbiome, potentially predisposing to respiratory infections.

Proton pump inhibitor use and nutritional deficiencies

Chronic use of proton pump inhibitors (PPIs) has been linked to hypomagnesemia [20]. This condition can lead to a range of symptoms, from muscle cramps and paresthesia to migraines and, in severe cases, life-threatening arrhythmias such as Torsade de pointes. Research indicates that the risk of hypomagnesemia is exacerbated when PPIs are used in conjunction with other medications, a situation known as polypharmacy, which is common in the geriatric population. Moreover, the severity of magnesium depletion appears to be dose-dependent [21], with higher doses of PPIs associated with greater reductions in magnesium levels.

Proton pump inhibitors (PPIs) have a notable impact on calcium absorption, which is a critical factor for maintaining bone health, particularly in the geriatric population [7]. The mechanism behind this is tied to the suppression of gastric acid production by PPIs. Gastric acid plays a crucial role in solubilizing calcium salts, such as calcium carbonate, which is a common form of calcium in supplements and certain foods. When gastric acid levels are diminished due to PPI use, the solubility and, consequently, the absorption of calcium carbonate is significantly reduced. This can lead to a state of calcium deficiency over time. Adequate calcium is essential not just for bone mineralization but also for vital physiological functions such as vascular contraction, muscle func-

tion, and nerve transmission. The potential for calcium deficits becomes particularly concerning for the elderly, who are already at an increased risk for osteoporosis and bone fractures. This risk is compounded by the fact that aging is associated with a natural decline in gastric acid production, which, when combined with PPI therapy, can lead to even more pronounced impairments in calcium absorption.

Vitamin B12 deficiency is another potential hazard of chronic PPI therapy, especially in the geriatric cohort. Despite the plethora of studies drawing this correlation, the data is not definitive, leaving this issue mired in controversy and inaction. Given these uncertainties, it would be prudent to periodically monitor vitamin B12 levels in long-term PPI users, especially older adults with compromised nutritional status and lower baseline vitamin reserves [7].

Lastly, the long-term impact of PPIs on iron absorption remains relatively uncharted territory, with sparse and inconsistent findings [7]. This gap in knowledge warrants further investigation to elucidate the full spectrum of nutritional implications associated with chronic PPI therapy.

PPIs and the Cardiovascular system

Prolonged PPI use has been associated with deleterious cardiovascular outcomes, including myocardial infarction, stroke, and heightened cardiovascular mortality. These associations are particularly pronounced with high-dose, long-term therapy.

Recent studies have identified an association between the administration of PPIs with clopidogrel and an increase in short-term mortality and an escalation in major adverse cardiac events (MACE), such as myocardial infarction and stent thrombosis [22]. This interaction is thought to arise from the inhibitory effect of certain PPIs on the enzyme CYP2C19, pivotal for the conversion of clopidogrel into its active metabolite. When this metabolic activation is hindered, clopidogrel's antiplatelet efficacy diminishes, elevating the risk of thrombotic events.

The pathophysiological underpinnings of PPI-related cardiovascular complications are multifaceted, encompassing endothelial dysfunction, premature senescence, nitric oxide depletion in endothelial cells, hypomagnesemia, and chromogranin A (CgA) elevation, all contributing to the cardiovascular risk profile. This growing body of evidence necessitates a reevaluation of PPI safety, particularly in patients with preexisting cardiovascular conditions [22].

Microbiome Alterations: PPIs can significantly alter the gut microbiome, and emerging evidence suggests that these changes might contribute to cardiovascular risk. Certain gut bacteria are known to produce metabolites like trimethylamine N-oxide (TMAO), which has been linked to atherosclerosis and cardiovascular disease. By altering the gut flora, PPIs could potentially influence the levels of these metabolites [22].

Endothelial Dysfunction: PPIs have been implicated in causing endothelial dysfunction, a key early step in the development of atherosclerosis. This could be mediated through several mechanisms, including oxidative stress and inflammation [22].

Vitamin Deficiencies: Chronic use of PPIs has been linked to deficiencies in key nutrients like magnesium and B vitamins, which play crucial roles in cardiovascular health. For instance, magnesium is essential for maintaining vascular tone and blood pressure, while B vitamins are vital for homocysteine metabolism, with elevated homocysteine levels being a known risk factor for cardiovascular diseases [22].

Direct Vascular Effects: There is some evidence to suggest that PPIs might have direct effects on the vasculature. For instance, PPIs have been shown to reduce nitric oxide production in endothelial cells, which is essential for vascular relaxation and maintaining blood pressure [22].

Inflammatory Pathways: Chronic inflammation is a known contributor to cardiovascular disease, and some studies have suggested that PPIs could exacerbate inflammatory pathways, potentially contributing to an increased cardiovascular risk [22].

Interactions with Other Cardiovascular Drugs: Beyond antiplatelet agents, PPIs can interact with other cardiovascular medications, potentially leading to suboptimal treatment outcomes. For example, they can affect the absorption and metabolism of certain statins, beta-blockers, and other drugs commonly used in cardiovascular disease management [22].

The impact of PPI use on the nervous system

Gray et al. [23] conducted a prospective cohort study that revealed no significant link between PPI exposure and the development of dementia or Alzheimer's disease (AD). This finding was supported by multivariable Cox regression analysis. However, other research presents a less definitive conclusion. Studies [24] investigating the correlation between PPI therapy and dementia have been inconclusive, hindered by potential unmeasured and residual confounding factors, as well as an incomplete understanding of the relevant biological mechanisms. Contrastingly, certain investigations [25] indicate that PPI users may have a reduced risk (15–23%) of deve-

loping dementia and cognitive decline (DCD) and could experience a delay in the onset of these conditions compared to non-users. This was observed in a retrospective analysis of community-dwelling patients aged 65 or older who were newly diagnosed with DCD.

Yet, other researchers [26,27] have identified a potential association between long-term PPI use and the onset of dementia, particularly among individuals who are APOE ε4 heterozygotes, as well as an increased risk of depression.

The relationship between PPI use and the occurrence of first-time ischemic stroke among the elderly was also examined [28]. While the total and annual occurrence rates of first-time ischemic stroke did not differ significantly between PPI users and non-users, there was an association with lower rates of stroke in PPI users.

PPIs can lead to vitamin B12 deficiency, which is crucial for maintaining healthy nerve cells and cognitive function [26]. A deficiency in B12 can lead to neurological issues, including memory problems, which could be mistaken for dementia. Chronic use of PPIs may influence inflammatory pathways in the body. Since neuroinflammation is implicated in various neurodegenerative diseases, this could potentially affect the CNS. The differential impact of PPIs on dementia risk among APOE ε4 heterozygotes suggests a complex interplay between genetics, medication use, and disease development [27].

Effect on the gastric mucosa

Proton pump inhibitors (PPIs) exert direct effects on gastric mucosal cells. Prolonged PPI therapy can induce histopathological alterations, including parietal cell protrusion, cystic dilation of fundic glands, and foveolar epithelial hyperplasia. Gastroscopic examination may reveal fundic gland polyps, hyperplastic polyps, multiple white and flat elevated lesions, cobblestone-like mucosa, or black spots [29]. A study with over 11,000 participants in South Korea found an association between PPI use and gastric cancer, noting an elevated cancer risk irrespective of H. pylori eradication status [30]. Conversely, long-term PPI therapy did not demonstrate an increased risk of gastric cancer in a high-risk region when compared to histamine 2 receptor antagonists (H2RAs) [31]. This suggests that while PPIs may induce notable gastric mucosal changes, their impact on gastric cancer risk may vary depending on the population and comparative treatments.

Finally, by increasing gastric pH, PPIs can alter the gastric and intestinal microbiome, potentially leading to bacterial overgrowth and changes in the types of bacteria present.

Conclusion

Our review considers the inappropriate use of proton pump inhibitors (PPIs) within the geriatric population. While PPIs are undeniably effective in managing acid-related disorders, their overprescription and misuse may lead to adverse outcomes, ranging from minor side effects to serious complications that can significantly impact morbidity and hospitalization rates among elderly patients. These include complications of the musculoskeletal, renal, infectious, nutritional, cardiovascular, neurological, and gastric systems. These observations are particularly concerning given the vulnerability of older adults to polypharmacy and the compounding impact of age-related physiological changes. We hope our review will lead to more judicious use of PPIs through more stringent adherence to PPI indications. In addition, we hope our review discusses the opportunity for intervention through the reassessment and potential deprescription of PPI therapy.

In conclusion, while PPIs remain a cornerstone in the management of acid-related conditions, their use in geriatric populations demands careful consideration, regular monitoring, and a readiness to deprescribe when the risks outweigh the benefits. The findings of this review serve as a call to action for healthcare providers to critically evaluate PPI therapy in older adults, ensuring that its administration is justified, appropriate, and closely monitored to mitigate the risk of adverse outcomes.

Konflikt interesów / Conflict of interest
Brak/None

References

1. National Ambulatory Medical Care Survey: 2018 National Summary Tables; U.S. Department of Health and Human Services • Centers for Disease Control and Prevention • National Center for Health Statistics.
2. Koggel LM, Lantinga MA, Büchner FL et al. Predictors for inappropriate proton pump inhibitor use: observational study in primary care, Br J Gen Pract, 2022, doi: 10.3399/BJGP.2022.0178.

3. Williams S, Miller G, Khoury R, Grossberg GT. Rational deprescribing in the elderly, Ann Clin Psychiatry. 2019;31(2):144-52.
4. Helgadottir H, Bjornsson ES. Problems Associated with Deprescribing of Proton Pump Inhibitors, Int J Mol Sci. 2019. doi: 10.3390/ijms20215469.
5. Ka Seng Thong B, Ima-Nirwana S, Kok-Yong C. Proton Pump Inhibitors and Fracture Risk: A Review of Current Evidence and Mechanisms Involved, Int J Environ Res Public Health. 2019. doi: 10.3390/ijerph16091571.
6. Wei J, Chan AT, Zeng C et al. Association between proton pump inhibitors use and risk of hip fracture: A general population-based cohort study, Bone. 2020. doi: 10.1016/j.bone.2020.115502. Epub 2020 Jun 25.
7. Ito T, Robert T. Jensen RT, Association of Long-term Proton Pump Inhibitor Therapy with Bone Fractures and effects on Absorption of Calcium, Vitamin B12, Iron, and Magnesium, Curr Gastroenterol Rep. 2010. doi: 10.1007/s11894-010-0141-0.
8. Zeng C, Neogi T, Chan AT et al. Proton pump inhibitor therapy and risk of knee replacement surgery: a general population-based cohort study, Osteoarthritis Cartilage. 2022 doi: 10.1016/j.joca.2021.12.010.
9. Seppala LJ, van de Glind EMM, Daams JG et al. Fall-Risk-Increasing Drugs: A Systematic Review and Meta-analysis: III. Others, J Am Med Dir Assoc. 2018, doi: 10.1016/j.jamda.2017.12.099.
10. Hart E, Terry E Dunn TE, Steven Feuerstein et al. Proton Pump Inhibitors and Risk of Acute and Chronic Kidney Disease: A Retrospective Cohort Study, Pharmacotherapy. 2019, doi: 10.1002/phar.2235.
11. Lazarus B, Chen Y, Wilson FP et al. Proton Pump Inhibitor Use and the Risk of Chronic Kidney Disease, JAMA Intern Med. 2016, doi: 10.1001/jamainternmed.2015.7193.
12. Xie Y, Bowe B, Tingting Li et al. Long-term kidney outcomes among users of proton pump inhibitors without intervening acute kidney injury, Kidney Int. 2017, doi: 10.1016/j.kint.2016.12.021.
13. Arora P, Anu Gupta, Golzy M et al. Proton pump inhibitors are associated with increased risk of development of chronic kidney disease, BMC Nephrol. 2016, doi: 10.1186/s12882-016-0325-4.
14. Liu W, Wang J, Wang M et al. Association of proton pump inhibitor use with risk of kidney stones: an analysis of cross-sectional data from the US National Health and Nutrition Examination Survey (2007-2018), BMJ Open. 2023, doi: 10.1136/bmjopen-2023-075136.
15. Wai-Kit L, Walter W Chan WW, Proton pump inhibitor use and the risk of small intestinal bacterial overgrowth: a meta-analysis,Clin Gastroenterol Hepatol. 2013, doi: 10.1016/j.cgh.2012.12.011.
16. Lázaro-Pacheco IB, Servín-Caamańo AI, Pérez-Hernández JL et al. Proton pump inhibitors increase the overall risk of developing bacterial infections in patients with cirrhosis, Arq Gastroenterol. 2018, doi: 10.1590/S0004-2803.201800000-09.
17. Trifan A, Stanciu C, Girleanu I et al. Proton pump inhibitors therapy and risk of Clostridium difficile infection: Systematic review and meta-analysis, World J Gastroenterol. 2017, doi: 10.3748/wjg.v23.i35.6500.
18. Allison A. Lambert, Jennifer O. Lam,Julie J. Paik et al. Risk of Community-Acquired Pneumonia with Outpatient Proton-Pump Inhibitor Therapy: A Systematic Review and Meta-Analysis, PLoS One. 2015, doi: 10.1371/journal.pone.0128004.
19. Laheij RJF, Sturkenboom MCJM, Hassing RJ et al. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs, JAMA, 2004, doi: 10.1001/jama.292.16.1955.
20. van Orten-Luiten ACB, Janse A, Verspoor E et al. Drug use is associated with lower plasma magnesium levels in geriatric outpatients; possible clinical relevance, Clin Nutr. 2019, doi: 10.1016/j.clnu.2018.11.018
21. Srinutta T, Chewcharat A, Takkavatakarn K et al. Proton pump inhibitors and hypomagnesemia: A meta-analysis of observational studies, Medicine (Baltimore) . 2019, doi: 10.1097/MD.0000000000017788.
22. Manolis AA, Manolis TA, Melita H et al. Proton pump inhibitors and cardiovascular adverse effects: Real or surreal worries? Eur J Intern Med . 2020, doi: 10.1016/j.ejim.2019.11.017.
23. Gray SL, Walker RL, Dublin S et al. Proton Pump Inhibitor Use and Dementia Risk: Prospective Population-Based Study, J Am Geriatr Soc. 2018, doi: 10.1111/jgs.15073.
24. Yang YX, Proton Pump Inhibitor Therapy and Dementia: What Is the Evidence? J Am Geriatr Soc . 2018, doi: 10.1111/jgs.15171.
25. Weiss A, Gingold-Belfer R, Boltin D et al. Chronic omeprazole use in the elderly is associated with decreased risk of dementia and cognitive decline, Dig Liver Dis. 2022, doi: 10.1016/j.dld.2021.11.018.

26. Novotny M, Klimova B, Valis M. PPI Long Term Use: Risk of Neurological Adverse Events? Front. Neurol, 2019, doi.org/10.3389/fneur.2018.01142
27. Zhang P, Li Z, Chen P et al. Regular proton pump inhibitor use and incident dementia: population-based cohort study, BMC Med. 2022, doi: 10.1186/s12916-022-02478-y.
28. Schmilovitz-Weiss H, Gingold-Belfer R, Peleg N et al. Use of proton pump inhibitors is associated with lower rates of first-time ischemic stroke in community-dwelling elderly, Br J Clin Pharmacol. 2021, doi: 10.1111/bcp.14488.
29. Ha Kim G, Proton Pump Inhibitor-Related Gastric Mucosal Changes, Gut Liver. 2021, doi: 10.5009/gnl20036.
30. Seo SI, Park CH, You S.C. et al. Association between proton pump inhibitor use and gastric cancer: a population-based cohort study using two different types of nationwide databases in Korea, Gut. 2021, doi: 10.1136/gutjnl-2020-323845.
31. Shin GY, Park JM, Hong J et al. Use of Proton Pump Inhibitors vs Histamine 2 Receptor Antagonists for the Risk of Gastric Cancer: Population-Based Cohort Study, Am J Gastroenterol. 2021, doi: 10.14309/ajg.0000000000001167.