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PROTON PUMP INHIBITORS IN FOCUS: FROM THE TREATMENT OF ACID-RELATED DISORDERS TO POTENTIAL RISKS

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Proton pump inhibitors (PPIs) represent one of the most commonly prescribed classes of medications used for the treatment of acid-related disorders and as a component of eradication therapy. Their efficacy in reducing gastric acid secretion and preventing complications has been repeatedly confirmed in both clinical practice and numerous studies. Despite their high effectiveness and relatively favorable safety profile in short-term use, PPIs have drawn increasing scientific attention due to the growing body of evidence regarding potential adverse effects associated with long-term administration. Impaired absorption of micronutrients, infections, dysbiosis, an elevated risk of osteoporotic fractures, and cardiovascular complications are among the potential concerns linked to these agents.

Furthermore, some studies suggest a possible association between prolonged PPI use and an increased risk of chronic kidney disease, dementia, and even malignancies. The mechanisms underlying these adverse effects remain a subject of ongoing debate, emphasizing the need for a judicious approach to prescribing PPIs. Increasing attention is being given to deprescribing strategies and the use of alternative methods for managing acid-related disorders. Another critical aspect is determining the optimal duration of therapy, individualized dose selection, and regular monitoring for potential complications. Future research aims to elucidate the long-term risks of PPI therapy and develop new strategies for their safer use. Thus, balancing the benefits and potential risks of PPIs remains a key challenge in gastroenterological practice.

A patient-centered approach plays a crucial role in mitigating risks, including educating patients on potential complications and the importance of adherence to PPI therapy recommendations. Additionally, the potential for combined therapeutic regimens, which allow for reduced dosage or dosing frequency, is actively being explored. A significant direction for future research involves the identification of novel pharmacological agents capable of effectively controlling acid secretion while minimizing adverse effects.

Key words: *acid-related disorders, proton pump inhibitors, mechanism of action, adverse effects, safety, risk, benefit.*

Людмила Каньовська, Альона Антонів, Юлія Яринич. Інгібітори протонної помпи у фокусі: від лікування кислотозалежних станів до потенційних ризиків

Інгібітори протонної помпи (далі – ІПП) є однією з найпоширеніших груп лікарських засобів, що застосовують для лікування кислотозалежних станів та схем ерадикаційної терапії. Їх ефективність у зниженні кислотності шлункового соку та профілактиці ускладнень була багаторазово підтверджена як у клінічній практиці, так і в численних дослідженнях. Попри високу ефективність і відносно сприятливий профіль безпеки при короткостроковому застосуванні, ІПП привернули увагу науковців через зростання кількості даних щодо можливих побічних ефектів при тривалому використанні. Порушення всмоктування мікроелементів, інфекції, дисбіоз, підвищення ризику остеопоротичних переломів і серцево-судинних ускладнень – це лише частина потенційних небезпек, асоційованих із цими препаратами.

Крім того, деякі дослідження вказують на можливий взаємозв'язок між тривалим прийомом ІПП та підвищеним ризиком хронічних захворювань нирок, деменції та навіть злоякісних новоутворень. Механізми цих побіч-

них ефектів залишаються предметом активних дискусій, що підкреслює необхідність зваженого підходу до призначення препаратів цієї групи. Дедалі більше уваги приділяється розробці стратегій депрескрайбінгу (відміни ІПП) та використанню альтернативних методів контролю кислотозалежних станів. Важливим аспектом є також визначення оптимальної тривалості терапії, індивідуальний добір дозування та регулярний моніторинг можливих ускладнень. Подальші дослідження мають на меті не лише детальніше оцінити довгострокові ризики ІПП, а й розробити нові підходи до їх безпечного використання. Так, баланс між користю та потенційними ризиками ІПП залишається ключовим питанням у гастроентерологічній практиці.

Значна роль у зменшенні ризиків належить пацієнтоорієнтованому підходу, який містить роз'яснення про можливі ускладнення та необхідність дотримання рекомендацій щодо застосування ІПП. Крім того, активно вивчається можливість використання комбінованих схем терапії, що дають змогу зменшити дозування або частоту прийому цих препаратів. Важливим напрямом майбутніх досліджень є пошук нових фармакологічних агентів, здатних ефективно контролювати кислотопродукцію зі зниженим профілем побічних ефектів.

Ключові слова: *кислотозалежні захворювання, інгібітори протонної помпи, механізм дії, побічні ефекти, безпека, ризик, користь.*

The urgency of the problem. Worldwide, the number of people suffering from gastrointestinal and hepatobiliary disorders is increasing annually, necessitating specialized gastroenterological care [1]. Risk factors for the development of these diseases include poor diet quality, nutritional imbalance, inadequate meal organization at home and work, psycho-emotional stress, self-medication, and delayed seeking of qualified medical assistance. Among gastroenterology patients, a significant proportion are affected by acid-related diseases (ARDs) of the digestive system, in which the acid-peptic factor plays a key role. This group includes peptic ulcer disease (PUD) of the stomach and duodenum, gastroesophageal reflux disease (GERD), chronic gastritis, NSAID-induced gastropathy, functional dyspepsia, symptomatic ulcers of the upper gastrointestinal tract, and Zollinger-Ellison syndrome, among others [4; 10; 13].

In younger patients, functional dyspepsia and duodenal peptic ulcers are more frequently observed, whereas in older age groups, gastroesophageal reflux disease, NSAID-induced gastropathy, and complicated forms of peptic ulcer disease predominate [11]. Since 1823, when William Prout identified hydrochloric acid as the primary component of gastric juice, numerous methods have been proposed to neutralize or reduce its production for the treatment of peptic ulcer disease and other gastroenterological conditions. The classification of acid-related diseases as a separate group highlights the critical role of gastric acid hypersecretion in their pathogenesis and underscores the primary therapeutic goal—reducing acid production [8]. Today, proton pump inhibitors (PPIs) hold a central position among acid-suppressive agents [7].

This class of drugs is widely used by physicians both in outpatient settings and in specialized gastroenterology and surgical departments. PPIs are among the most commonly prescribed medications in gastroenterology due to their high efficacy in treating acid-related disorders. However, alongside their widespread use, growing concerns have emerged regarding their potential adverse effects, particularly with long-term administration. As PPI prescriptions increase, concerns about their long-term safety are also rising (D. Freedberg et al., 2017) [7; 9; 12; 18]. As with other pharmacological agents, adverse reactions may occur even when PPIs are prescribed at doses recommended in medical guidelines. The most common side effects (reported in 1–10 % of patients) include headache, abdominal pain, constipation, diarrhea, bloating, nausea, and vomiting.

Recent studies suggest a possible association between prolonged PPI use and an increased risk of chronic kidney disease, dementia, and alterations in gut microbiota. Additionally, there is ongoing discussion about the potential impact of PPIs on the metabolism of vitamin B12, iron, and magnesium, which may contribute to deficiency-related conditions. Emerging research also indicates that long-term PPI therapy may lead to changes in gut microbiome composition, potentially increasing the risk of dysbiosis and infectious complications. Given these concerns, international clinical guidelines recommend careful assessment of the necessity of prolonged PPI use and periodic therapy reevaluation. Alternative approaches, such as the use of H2-receptor antagonists or individualized PPI dosing, are being explored as potential strategies to minimize adverse effects.

The purpose: of the study is to analyze scientific publications and research dedicated to the investigation of side effects associated with the use of proton pump inhibitors.

Research materials and methods: To develop a scientifically grounded review article, a systematic search of scientific publications was conducted in leading databases such as PubMed, Scopus, Google Scholar, Cochrane Library, and Web of Science.

The search utilized key terms including "proton pump inhibitors", "acid-dependent diseases", "gastri-

tis", "gastric ulcer", "esophageal reflux", "long-term use risks" and "adverse effects of proton pump inhibitors".

The publication search was limited to articles published from 2005 to the present to reflect the most recent advances in both science and clinical practice. The inclusion criteria for analysis were randomized controlled trials, review articles, meta-analyses, long-term cohort studies, and clinical trials evaluating the effectiveness and safety of proton pump inhibitors in the context of acid-dependent conditions. Articles that did not align with the topic or those with limited availability or insufficient methodological quality, were excluded. The research materials include a comprehensive review of both clinical studies and meta-analyses, aiming to thoroughly examine the effectiveness and safety of proton pump inhibitors in various contexts. This methodology provides a comprehensive perspective on the role of these medications in treating acid-dependent conditions and evaluating their potential long-term health risks for patients.

Research results and their discussion. By international recommendations for the treatment of acid-dependent diseases, such as gastroesophageal reflux disease (GERD), functional dyspepsia, peptic ulcers of the stomach and duodenum, proton pump inhibitors (PPIs) are used either as monotherapy or in combination with other medications. If the disease occurs against the backdrop of Helicobacter pylori infection or is one of its manifestations (chronic gastritis B, MALT lymphomas), PPIs are included in eradication therapy regimens. Additionally, PPIs play an essential role in the prevention and treatment of complications associated with bariatric surgeries, such as sleeve gastrectomy, gastric bypass, and biliopancreatic diversion. Their use aims to reduce the level of gastric acid secretion, prevent GERD, treat gastroduodenal ulcers, and prevent marginal ulcers at gastrointestinal anastomosis sites. Following bariatric surgeries, patients are at an increased risk of acid-dependent complications due to anatomical changes in the stomach, which contribute to reflux and decreased mucosal protective barriers, as well as elevated acidity in the remaining stomach portion.

Currently, PPIs remain the undisputed leaders among acid-secretion inhibitors. They are classified as follows:

1. Traditional first-generation PPIs: omeprazole, lansoprazole.
2. Traditional second-generation PPIs: pantoprazole, rabeprazole.
3. Immediate-release formulations (PPI + sodium bicarbonate).
4. Isomeric forms of PPIs: esomeprazole.
5. Isomeric forms of PPIs with modified dual-phase prolonged release: dexlansoprazole.
6. Combined formulations: PPI + H2-histamine blockers.
7. New benzimidazole and non-benzimidazole PPIs (ilaprazole, tenatoprazole).
8. K+-competitive acid blockers (vonoprazan). The last three groups are not yet available in Ukraine.

The primary mechanism of action is the inhibition of H+/K+ ATPase (proton pump) embedded in the apical membrane of parietal cells. The proton pump transports K+ ions into the cell and H+ ions out, leading to hydrochloric acid secretion. PPIs are derivatives of benzimidazole and are not active substances on their own but, after accumulating in the secretory canaliculi of parietal cells, are converted into sulfonamide derivatives that form covalent bonds with the SH groups of H+/K+ ATPase, thus inhibiting the enzyme's activity. The first drug in this group, omeprazole, was synthesized in 1979 and officially recommended for clinical use in 1988 at the World Congress in Rome.

Omeprazole is the reference and most researched PPI. Its bioavailability is 35–40 % after the first dose and 65 % after repeated administration. Rabeprazole's bioavailability does not change with dose repetition and is 52 %. Lansoprazole also has consistent bioavailability of 80–90 % in standard therapeutic doses, which decreases with lower doses. Esomeprazole's bioavailability is 64 % after the first dose and 89 % after repeated use. Food and antacid intake do not affect the bioavailability of these drugs. For pantoprazole, lansoprazole, and rabeprazole, there is a direct relationship between the administered dose and plasma drug concentration.

Recent studies show that the global prevalence of PPI use is increasing, particularly among the elderly. This may be due to numerous comorbidities, a higher risk of acid-related gastrointestinal disorders, polypharmacy, and a lack of treatment cessation. A recent study emphasizes the need to reduce inappropriate PPI use in individuals over 65 years old, highlighting the importance of discontinuing unnecessary PPI prescriptions in this population. Furthermore, approximately 65 % of patients prescribed PPIs do not require them (Hayes et al., 2019), which raises concerns about the overuse of these drugs and its implications for public health. The excessive use of PPIs, similar to the over-prescription of antibiotics, can disrupt the gut microbiome, leading to reduced diversity and richness of the gastrointestinal microbiota (Sun et al., 2019). Misuse of PPIs has been

associated with a range of adverse effects, including gastrointestinal infections, such as those caused by Salmonella, Campylobacter, and possibly Clostridium difficile in hospitalized patients.

Moreover, long-term use of PPIs has been linked to an increased risk of osteoporosis, particularly in older adults, and has a potential impact on the absorption of vitamin B12, contributing to neurological and hematological complications (Lam et al., 2013). PPIs are also associated with an elevated risk of chronic kidney disease (CKD) and acute interstitial nephritis. Studies show that the absolute risk of kidney damage due to PPIs is 0.1–0.3 % per patient per year (Freedberg et al., 2017). After discontinuing PPIs and initiating corticosteroid therapy, the prognosis is favorable, with complete recovery in many cases.

Additionally, proton pump inhibitors (PPIs) are associated with an increased risk of gastrointestinal infections due to their acid-suppressing effects, which reduce the stomach's natural defense against pathogens. Studies have shown that PPI use is linked to a higher incidence of infections caused by *Clostridium difficile*, a harmful bacterium that can lead to severe diarrhea and colitis. In patients with long-term PPI use, the risk of developing hypomagnesemia, which can lead to muscle cramps, arrhythmias, and seizures, is also heightened. Furthermore, the long-term suppression of stomach acid has been shown to interfere with the absorption of other essential minerals, such as calcium and iron, contributing to deficiencies and potential bone fractures. Research indicates that stopping PPIs abruptly can lead to rebound acid hypersecretion, causing symptoms of reflux to worsen temporarily. As such, gradual tapering of PPI therapy is recommended to minimize this risk, particularly for patients who have been on long-term treatment.

Conclusions. Proton pump inhibitors (PPIs) are highly effective agents for the treatment of acid-dependent diseases, but their long-term use can be associated with a range of side effects. Given the significant role of PPIs in clinical practice, it is crucial to balance their effectiveness with potential adverse effects. An important aspect of therapy involves an individualized approach to dosage selection, duration of treatment, and regular monitoring of the patient's condition, which helps minimize negative outcomes and improve overall clinical results.

Future research directions: Long-term studies are necessary for a more detailed understanding of the prolonged effects of PPI use, particularly their impact on the risk of cardiovascular diseases, oncological conditions, and metabolic disorders. Investigating the genetic and molecular mechanisms by which PPIs affect the body could aid in developing personalized treatment approaches, including selecting the optimal drug and dosage based on the individual characteristics of the patient. These research areas will contribute to enhancing the quality of patient care, ensuring safer use of PPIs, and developing new therapeutic strategies for the treatment of acid-dependent diseases.

BIBLIOGRAPHY

1. New Zealand Formulary (NZF) (2021) New Zealand Formulary (NZF), NZF v[114]. Available from: www.nzf.org.nz. Accessed 1 Dec 2021.

2. National Institute for Health and Care Excellence (NICE) (2019) Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management. Clinical guideline (CG184). Available from: https://www.nice.org.uk/guidance/cg184/chapter/Appendix-A-Dosage-information-on-proton-pump-inhibitors. Accessed on 1 Dec 2021.

3. Hu X, You X, Sun X, Lv J, Wu Y, Liu Q et al. (2018) Off-label use of proton pump inhibitors and economic burden in the Chinese population: a retrospective analysis using claims database. *Value in Health*, 21:S82–S83. https://doi.org/10.1016/j.jval.2018.05.010

4. Ding J, Heller DA, Ahern FM, Brown TV (2014) The relationship between proton pump inhibitor adherence and fracture risk in the elderly. *Calcified Tissue International*, 94(6):597–607. https://doi.org/10.1007/s00223-014-9937-9

5. Doell A, Walus A, To J, Bell A (2018) Quantifying candidacy for deprescribing of proton pump inhibitors among long-term care residents. *Canadian Journal of Hospital Pharmacy*, 71(5):302–307. https://doi.org/10.4212/cjhp.v71i5.3019

6. Fattahi MR, Niknam R, Shams M, Anushiravani A, Taghavi SA, Omrani GR et al. (2019) The association between prolonged proton pump inhibitors use and bone mineral density. *Risk Management and Healthcare Policy*, 12:349–355. https://doi.org/10.2147/RMHP.S203234

7. Gendre P, Mocquard J, Artarit P, Chaslerie A, Caillet P, Huon JF (2022) (De)Prescribing of proton pump inhibitors: what has changed in recent years? An observational regional study from the French health insurance database. *BMC Primary Care*, 23(1):341. https://doi.org/10.1186/s12875-022-01891-7

8. Gray SL, Walker RL, Dublin S, Yu O, Aiello Bowles EJ, Anderson ML et al. (2018) Proton pump inhibitor use and dementia risk: prospective population-based study. *Journal of the American Geriatrics Society (JAGS)*, 66(2):247–253. https://doi.org/10.1111/jgs.15162

9. Hendrix I, Page AT, Korhonen MJ, Bell JS, Tan ECK, Visvanathan R et al. (2019) Patterns of high-dose and long-term proton pump inhibitor use: a cross-sectional study in six South Australian residential aged care services. *Drugs – Real World Outcomes*, 6(3):105–113. https://doi.org/10.1007/s40001-019-00210-5

10. Koggel LM, Lantinga MA, Büchner FL, Drenth JPH, Frankema JS, Heeregrave EJ et al. (2022) Predictors for inappropriate proton pump inhibitor use: observational study in primary care. *British Journal of General Practice*, 72(725):e899–e906. https://doi.org/10.3399/BJGP.2021.0863

11. Lassalle M, Le Tri T, Bardou M, Biour M, Kirchgesner J, Rouby F et al. (2019) Use of proton pump inhibitors in adults in France: a nationwide drug utilization study. *European Journal of Clinical Pharmacology*, 76(3):449–457. https://doi.org/10.1007/s00228-019-02799-5

12. Maes ML, Fixen DR, Linnebur SA (2017) Adverse effects of proton-pump inhibitor use in older adults: a review of the evidence. *Therapeutic Advances in Drug Safety*, 8(9):273–297. https://doi.org/10.1177/2042098617722565

13. Dills H, Shah K, Messinger-Rapport B, Bradford K, Syed Q (2018) Deprescribing medications for chronic disease management in primary care settings: a systematic review of randomized controlled trials. *Journal of the American Medical Directors Association*, 19(11):923-935.e2. https://doi.org/10.1016/j.jamda.2018.04.015

14. Lassalle M, Le Tri T, Bardou M, Biour M, Kirchgesner J, Rouby F et al. (2019) Use of proton pump inhibitors in adults in France: a nationwide drug utilization study. *European Journal of Clinical Pharmacology*, 76(3):449–457. https://doi.org/10.1007/s00228-019-02799-5

15. Guillot J, Maumus-Robert S, Marceron A, Noize P, Pariente A, Bezin J (2020) The burden of potentially inappropriate medications in chronic polypharmacy. *Journal of Clinical Medicine*, 9(11):3728. https://doi.org/10.3390/jcm9113728

16. Rababa M, Rababa'h A (2021) The inappropriate use of proton pump inhibitors and its associated factors among community-dwelling older adults. *Heliyon*, 7(7):e07595. https://doi.org/10.1016/j.heliyon.2021.e07595

17. Dills H, Shah K, Messinger-Rapport B, Bradford K, Syed Q (2018) Deprescribing medications for chronic disease management in primary care settings: a systematic review of randomized controlled trials. *Journal of the American Medical Directors Association*, 19(11):923-935.e2. https://doi.org/10.1016/j.jamda.2018.04.015

18. Farrell B, Pottie K, Thompson W, Boghossian T, Pizzola L, Rashid FJ et al. (2017) Deprescribing proton pump inhibitors: Evidence-based clinical practice guideline. *Canadian Family Physician*, 63(5):354–364. https://doi.org/10.1278/cfp.2017.0134

19. Yap MH, Yip G, Edwards A, D'Intini V, Tong E (2019) Appropriateness of proton pump inhibitor use in patients admitted under the general medical unit. *Journal of Pharmacy Practice and Research*, 49(5):447–453. https://doi.org/10.1002/jppr.1537

20. Wei J, Chan AT, Zeng C, Bai X, Lu N, Lei G et al. (2020) Association between proton pump inhibitors use and risk of hip fracture: a general population-based cohort study. *Bone (New York, NY)*, 139:115502. https://doi.org/10.1016/j.bone.2020.115502

REFERENCES

1. New Zealand Formulary (NZF) (2021) New Zealand Formulary (NZF), NZF v[114]. Available from: www.nzf.org.nz. Accessed 1 Dec 2021.

2. National Institute for Health and Care Excellence (NICE) (2019) Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management. Clinical guideline (CG184). Available from: https://www.nice.org.uk/guidance/cg184/chapter/Appendix-A-Dosage-information-on-proton-pump-inhibitors. Accessed on 1 Dec 2021.

3. Hu X, You X, Sun X, Lv J, Wu Y, Liu Q et al. (2018) Off-label use of proton pump inhibitors and economic burden in the Chinese population: a retrospective analysis using claims database. *Value in Health*, 21:S82–S83. https://doi.org/10.1016/j.jval.2018.05.010

4. Ding J, Heller DA, Ahern FM, Brown TV (2014) The relationship between proton pump inhibitor adherence and fracture risk in the elderly. *Calcified Tissue International*, 94(6):597–607. https://doi.org/10.1007/s00223-014-9937-9

5. Doell A, Walus A, To J, Bell A (2018) Quantifying candidacy for deprescribing of proton pump inhibitors among long-term care residents. *Canadian Journal of Hospital Pharmacy*, 71(5):302–307. https://doi.org/10.4212/cjhp.v71i5.3019

6. Fattahi MR, Niknam R, Shams M, Anushiravani A, Taghavi SA, Omrani GR et al. (2019) The association between prolonged proton pump inhibitors use and bone mineral density. *Risk Management and Healthcare Policy*, 12:349–355. https://doi.org/10.2147/RMHP.S203234

7. Gendre P, Mocquard J, Artarit P, Chaslerie A, Caillet P, Huon JF (2022) (De)Prescribing of proton pump inhibitors: what has changed in recent years? An observational regional study from the French health insurance database. *BMC Primary Care*, 23(1):341. https://doi.org/10.1186/s12875-022-01891-7

8. Gray SL, Walker RL, Dublin S, Yu O, Aiello Bowles EJ, Anderson ML et al. (2018) Proton pump inhibitor use and dementia risk: prospective population-based study. *Journal of the American Geriatrics Society (JAGS)*, 66(2):247–253. https://doi.org/10.1111/jgs.15162

9. Hendrix I, Page AT, Korhonen MJ, Bell JS, Tan ECK, Visvanathan R et al. (2019) Patterns of high-dose and long-term proton pump inhibitor use: a cross-sectional study in six South Australian residential aged care services. *Drugs – Real World Outcomes*, 6(3):105–113. https://doi.org/10.1007/s40001-019-00210-5

10. Koggel LM, Lantinga MA, Büchner FL, Drenth JPH, Frankema JS, Heeregrave EJ et al. (2022) Predictors for inappropriate proton pump inhibitor use: observational study in primary care. *British Journal of General Practice*, 72(725):e899–e906. https://doi.org/10.3399/BJGP.2021.0863

11. Lassalle M, Le Tri T, Bardou M, Biour M, Kirchgesner J, Rouby F et al. (2019) Use of proton pump inhibitors in adults in France: a nationwide drug utilization study. *European Journal of Clinical Pharmacology*, 76(3):449–457. https://doi.org/10.1007/s00228-019-02799-5

12. Maes ML, Fixen DR, Linnebur SA (2017) Adverse effects of proton-pump inhibitor use in older adults: a review of the evidence. *Therapeutic Advances in Drug Safety*, 8(9):273–297. https://doi.org/10.1177/2042098617722565

13. Dills H, Shah K, Messinger-Rapport B, Bradford K, Syed Q (2018) Deprescribing medications for chronic disease management in primary care settings: a systematic review of randomized controlled trials. *Journal of the American Medical Directors Association*, 19(11):923-935.e2. https://doi.org/10.1016/j.jamda.2018.04.015

14. Lassalle M, Le Tri T, Bardou M, Biour M, Kirchgesner J, Rouby F et al. (2019) Use of proton pump inhibitors in adults in France: a nationwide drug utilization study. *European Journal of Clinical Pharmacology*, 76(3):449–457. https://doi.org/10.1007/s00228-019-02799-5

15. Guillot J, Maumus-Robert S, Marceron A, Noize P, Pariente A, Bezin J (2020) The burden of potentially inappropriate medications in chronic polypharmacy. *Journal of Clinical Medicine*, 9(11):3728. https://doi.org/10.3390/jcm9113728

16. Rababa M, Rababa'h A (2021) The inappropriate use of proton pump inhibitors and its associated factors among community-dwelling older adults. *Heliyon*, 7(7):e07595. https://doi.org/10.1016/j.heliyon.2021.e07595

17. Dills H, Shah K, Messinger-Rapport B, Bradford K, Syed Q (2018) Deprescribing medications for chronic disease management in primary care settings: a systematic review of randomized controlled trials. *Journal of the American Medical Directors Association*, 19(11):923-935.e2. https://doi.org/10.1016/j.jamda.2018.04.015

18. Farrell B, Pottie K, Thompson W, Boghossian T, Pizzola L, Rashid FJ et al. (2017) Deprescribing proton pump inhibitors: Evidence-based clinical practice guideline. *Canadian Family Physician*, 63(5):354–364. https://doi.org/10.1278/cfp.2017.0134

19. Yap MH, Yip G, Edwards A, D'Intini V, Tong E (2019) Appropriateness of proton pump inhibitor use in patients admitted under the general medical unit. *Journal of Pharmacy Practice and Research*, 49(5):447–453. https://doi.org/10.1002/jppr.1537

20. Wei J, Chan AT, Zeng C, Bai X, Lu N, Lei G et al. (2020) Association between proton pump inhibitors use and risk of hip fracture: a general population-based cohort study. *Bone (New York, NY)*, 139:115502. https://doi.org/10.1016/j.bone.2020.115502