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Review Article

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Adverse Drug Reactions of Proton Pump Inhibitors: A Review

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Abstract

Proton pump inhibitors (PPIs) are frequently utilized for the treatment of a range of stomach disorders, but like any medication, they can cause adverse reactions. The benefits of taking these drugs generally outweigh the risks, but Potential adverse effects should be taken into consideration. This review will present updated information on the negative reactions associated with PPIs and identify areas for further research. The research for this paper was gathered from a variety of sources, including Google Scholar, Science Direct, PubMed and other journals published between 1998 and 2022.

KEYWORDS
Bone status, Cancer, Dementia, Proton pump inhibitors, Vit. B12.

INTRODUCTION

According to guidelines on good pharmacovigilance practices, an adverse drug reaction (ADR) is a negative, unexpected outcome resulting from the use of medication. It can happen after taking a single dose or after taking a drug for an extended period, or as a result of simultaneous use of multiple medications. ADR is different from the term "side effect," as the later can be both helpful and harmful but the former is always harmful (Nebeker *et al*., 2004). Pharmacovigilance is the field that focuses on the study of adverse drug reactions.

PPIs, first introduced in 1989, are now commonly used worldwide and have been approved by the FDA for treating various gastric disorders such as peptic ulcers and acid reflux, as well as preventing stomach bleeding in patients taking anti-platelets medication PPIs inhibit the production of stomach acid and have been known to cause abdominal pain, diarrhea, and headaches as side effects. While they have generally been considered safe, recent studies have shown that using these medications for a long period of time may be linked to a heightened risk of Clostridium difficile diarrhea, fractures, pneumonia, low levels of magnesium, a lack of vitamin B12, kidney disease, and dementia. Researchers are currently looking further into these possible risks for individuals who take PPIs for a long time. Although there is a significant amount of research available, it is not enough to prove a direct link between using proton pump inhibitors and experiencing severe negative effects. However, when it is deemed necessary for medical treatment, PPIs can be prescribed in small doses to alleviate symptoms (Nehra *et al*., 2018).

PPIs and stomach cancer

A study by Bridoux *et al*. (2022) showed that latest meta-analyses, reviews and clinical trials have revealed two opposing effects of PPIs on tumor activity which includes stimulating tumor growth by increasing the level of plasma gastrin or suppressing tumor growth by blocking V-ATPases.

The most likely explanation for the association between taking PPI medication for an extended period and the occurrence of stomach cancer is through an increase in the gastrin level resulting from a decrease in the amount of stomach acid being produced (Lundell *et al*., 2015). The hormone gastrin promotes the expansion, movement, self-digestion, and survival of cancer cells (Rao *et al*., 2017).

Furthermore, Cheung and Leung suggested that prolonged use of proton pump inhibitors could potentially lead to stomach cancer due to an elevation in the gastric gastrin levels, a rise in enterochromaffin-like cells (ECL) and an overgrowth of bacteria in the stomach.

PPIs can cause a decrease in stomach acid which leads to the growth of ECL cells. These cells are specifically affected by the hormone gastrin in the stomach lining and are linked to the development of certain receptors and tumors. Additionally, using PPIs for a prolonged period of time, particularly in those with H. pylori infections, can worsen gastritis and increase the risk of gastric malignancy triggered by inflammation and abnormal cell growth (Waldum *et al*., 2018).

Somatostatin controls gastrin secretion from antral G-cells in a negative feedback mechanism. However, this process can be disrupted by prolonged use of PPIs as well as other acid-reduc-

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ing drugs, which can lead to low stomach acidity. This can cause an excessive amount of gastrin to be released, resulting in the growth of the stomach lining and the development of ECL cells (Feng *et al*., 2010).

Based on previous observational research results, a recent meta-analysis reexamined the relation between taking PPIs and the risk of developing gastric malignancies. The study also analyzed any potential bias and looked at how well the observational associations held up when accounting for factors that were not measured. Thirteen of the observational studies reported an 80% higher risk of developing stomach malignancy among those using PPIs (95% CI: 1.46–2.22 RR, 1.80) than those who do not take them (Poly *et al*., 2022).

Two retrospective cohort studies, conducted by Cheung *et al*. (2018) and Niikura *et al*. (2018), suggested a deteriorating effect of the prolonged administration of PPIs on atrophic gastritis and intestinal metaplasia in individuals who received H. pylori eradicating therapy. The studies suggest that the hypochlorhydria caused by PPIs can exacerbate pre-existing gastric damage caused by H. pylori and may also increase the risk of turning pre-existing precancerous lesions into gastric cancer.

Interestingly, multiple studies have shown that PPIs can decrease the resistance of gastric cancerous cells to chemotherapy by changing the acidity of the microenvironment, reducing cancer stemness, and affecting the signal transducer and activator of transcription 3 (STAT3) signaling pathway. The inhibitory effect of PPIs on STAT3 activity could be beneficial in overwhelming drug resistance and enhancing the effectiveness of chemotherapy. Additionally, PPIs may play a "dual role" in both the development and the treatment of stomach malignancies Joo *et al*., 2019).

The pH levels within the environment surrounding a tumor can vary, with solid tumors typically having an acidic extracellular pH and a neutral to alkaline intracellular pH, while the microenvironment in healthy tissues typically remains alkaline (Lee and Tannock, 1998).

The presence of acidic conditions within cells leads to decreased effectiveness of certain cytotoxic medications, including doxorubicin, 5-fluorouracil, vinblastine and cisplatin (De Milito and Fais, 2005).

PPIs can help overcome resistance to drugs and improve the effectiveness of chemotherapy by blocking the V-H+ -ATPase in malignant cells, making the microenvironment of the tumor more alkaline and keeping drugs that are weakly basic inside the cells they are targeting (De Milito *et al*., 2010).

Several laboratory studies have shown that when gastric cancer cells are treated with PPIs before inhibiting the V-H+ -ATPase enzyme, certain downstream effects occur. These effects include the decrease in phosphorylation of LRP6 as well as the suppression of the signaling pathways of Wnt/β-catenin or PI3K/Akt/mTOR/HIF-1α (Shen *et al*., 2013; Chen *et al*., 2018).

The way cancer stem cells behave, also known as cancer stemness, has a role in both the poor response of cancer to chemotherapy and in the spread of cancer to other parts of the body (metastasis) (Chen *et al*., 2017).

Cancer stem cells (CSCs) are able to produce family proteins of ATP binding cassette (ABC) transporters that aid in multidrug resistance (MDR) by increasing the activity of drug efflux pumps. Examples of these transporters include Pglycoprotein, multi-drug resistance associated protein-1 (MRP-1), lung resistance protein (LRP) and breast cancer resistance protein (BCRP). PPIs can lower chemoresistance in solid cancer cells by altering anaerobic glycolysis and ABC transporters (Kim *et al*., 2017).

An *in vivo* and *in vitro* study revealed that the use of pantoprazole specifically triggered the process of cell death through apoptosis in cancerous cells found in the stomach, while the healthy cells in the stomach remained unharmed (Yeo *et al*., 2004).

A study found that administering high doses of esomeprazole downregulates the release of exosomes as well as the exosome-related micro-RNAs like miR-3934-5p, miR-6126 and miR-494-3p. These micro-RNAs are linked to tumor adhesion, invasion, migration, and metastasis in gastric cancer cells. Esomeprazole can also regulate the HIF-1α-FOXO1 axis which in turn induces apoptosis, inhibit cellular migration and invasion, which are the mechanisms that cancer cells use to spread (Guan *et al*., 2017).

The possibility of a link between proton pump inhibitors and stomach malignancy has been suggested by the context of their relationship, but studies on this topic have yielded mixed results. Some have found a 2.4-fold higher risk, but others couldn't detect differences in the incidence of stomach malignancies among chronic users of PPIs compared to those who do not, regardless of whether they have the bacteria H. pylori. The evidence supporting this hypothesis comes mainly from observational studies, and there is a need for more robust information to confirm the relationship (Chinzon *et al*., 2022).

PPIs and dementia

Dementia is a condition marked by a steady decline in mental abilities and the ability to perform daily tasks. The most common dementia types are vascular dementia, Alzheimer's disease, frontotemporal dementia, and Lewy body dementia. In 2010, an estimate of 35.6 million dementia cases were reported around the world with a speculation to reach 65.7 million by 2030 (Prince *et al*., 2013).

The accumulation of amyloid-beta (Aβ) in the brain is a key event in the progression of Alzheimer's disease. This buildup is caused by the gradual cleavage of the amyloid precursor protein (APP) by enzymes called beta-secretase (β-site APP-cleaving enzyme 1 (BACE1)) and gamma-secretase. In addition, Badiola al. (2013) examined the effectiveness of PPIs on the production of Aβ, the activity of γ-secretase and BACE1 utilizing both *in vitro* and *in vivo* model systems of AD. They discovered that PPI (lansoprazole) can worsen BACE1 activity and cause an increase in the levels of Aβ40 and Aβ37. Furthermore, lansoprazole also modified the γ-secretase cutting point by functioning as a γ-secretase modulator (iGSM), resulting in a rise in the levels of Aβ42.

In a large study of a population, Zhang and colleagues found that using PPIs was linked to a greater chance of developing dementia. The study specifically showed that regular use of PPIs was linked to the onset of all dementia types, including vascular dementia and Alzheimer's disease, especially in individuals who had a specific genetic variation called apolipoprotein E ε4 (APOE ε4). The study also found that the risk of dementia was especially high in individuals who both used PPIs and had the APOE ε4 genetic variation (Zhang *et al*., 2022).

A relationship was detected between proton PPIs and the deficiency of vitamin B12, which can lead to an excessive amount of homocysteine in the blood. Both a deficiency of vitamin B12 and homocysteinemia were reported to increase the risk of cognitive decline, shrinking of the brain, and dementia (Ma *et al*., 2017).

Research has evaluated the relation between the risk to develop dementia, whether Alzheimer's disease (AD) or non-Alzheimer's disease (non-AD), and the use of PPIs. An association was spotted and was positively proportionate to the number of PPIs used, the bigger the number, the higher the risk. However, the difference in the risk was insignificant in the AD group unlink the non-AD group (Torres-Bondia *et al*., 2020).

Wu *et al*. (2021) conducted a thorough examination of spontaneous reports submitted to the FAERS database in 2021. The United States Food and Drug Administration Adverse Event Reporting System (FAERS) is a widely accessible database that contains over twelve million reported adverse events from both healthcare professionals and non-professionals. Through data mining techniques, the FAERS can be utilized to identify potential adverse events related to medication use. They couldn't link the intake of PPIs, such as rabeprazole, esomeprazole, dexlansoprazole, lansoprazole, pantoprazole and omeprazole, to the development of dementia. Therefore, based on the FAERS data, discontinuing PPI treatment should not be considered as a factor in preventing dementia events.

PPIs and Vit. B12

The effect of PPIs on vitamin B-12 levels in the body is connected to the stomach's acidity, which is necessary for breaking down food and releasing vitamin B-12 from protein. The acid helps to activate the conversion of pepsinogen to pepsin, which is responsible for separating vitamin B-12 from food proteins. When there is a shortage of stomach acid because of PPI usage, the body's ability to extract vitamin B-12 from foods is reduced, leading to a reduction in the absorbed vitamin B-12 (Miller, 2018).

Previous research on investigating the link between the intake of PPIs and vitamin B-12 levels has been limited and often relied on only one type of biomarker. However, experts agree that relying solely on one biomarker for vitamin B-12 deficiency is not reliable and that using multiple biomarkers, such as both functional markers (homocysteine and methylmalonic acid) and direct markers (total vitamin B-12 and holotranscobalamin) should be employed to diagnose deficiency (Fedosov *et al*., 2015).

Porter *et al*. (2021) investigated the relationship between vitamin B-12 levels and both the intake of PPIs and atrophic gastritis. They also examined the impact of consuming fortified foods. The study found that individuals who took higher doses of PPIs (≥30 mg/d) had significantly lower levels of holotranscobalamin (holoTC) and a higher prevalence of vitamin B-12 deficiency than those who did not take PPIs (25% compared to 15%). The study also found a direct positive association between the risk of developing vitamin B-12 deficiency and the dose of PPIs. However, the study also showed that regularly consuming fortified foods can improve one's vitamin B-12 status.

The results of this study align with those found in the recent research conducted by Mumtaz *et al*. (2022) who reported vitamin B-12 deficiency in more than half of the male cases (55.10%). Furthermore, it was discovered that individuals taking Omeprazole had lower vitamin B12 levels compared to those taking Pantoprazole. The research suggests that using PPIs for a long period increases the risk of vitamin B12 deficiency which is more evident among males who are 18-40 years old.

Another study found that long-term use of acid-reducing medications as PPIs or H2 blockers may lead to low levels of vitamin B-12 in blood. This deficiency is seen in both drug groups and is not dependent on the specific medication being used, such as pantoprazole or omeprazole. Therefore, it is important to note that acid suppression in general can cause vitamin B12 deficiency independent of the type of used drug (Damodharan *et al*., 2021).

Another study studied the link between taking proton pump inhibitors for one year in people who were new to the medication and any changes in their vitamin B12 levels. The study also looked to see if this relationship varied among four specific PPI drugs. The findings revealed that PPI usage did not cause a clinically significant deficiency in vitamin B12. Also, only 2.9% of the participants were diagnosed with a vitamin B12 deficiency, and there were no significant variations between those who used PPIs and those who did not (Qorraj-Bytyqi *et al*., 2018).

Based on a recent extensive research, there is no association between taking PPI medication and having deficiencies in vitamin B12 or high levels of homocysteine. The study found that patients who take PPI medication may have slightly increased vitamin B12 and homocysteine levels which are not significant enough to cause any health concerns (Lerman *et al*., 2022).

Similarly, a research study that compared different groups of patients with peptic ulcer disease revealed insignificant difference in the levels of Vitamin B12 among those who regularly used PPIs for a long period of time and those who did not use them. Therefore, the study suggests that doctors should be careful and thoughtful when prescribing long-term PPIs (Rahamn *et al*., 2021).

PPI and bone status

Several observational studies revealed inconsistent findings regarding the link between PPIs and a reduced bone mineral density.

In 2010, the FDA issued a statement cautioning about the possibility of increasing the risk of fractures in the hip, wrist and spine with prolonged PPIs usage (FDA, 2011).

Recent studies have shown that using PPIs for extended periods of time may trigger osteoporosis, particularly hip fracture. This is believed to occur due to the disruption of various biological pathways that affect bone density. The overuse of PPIs has been shown to negatively impact bone density and overall bone health (Hussain and Mazumder, 2021).

Calcium is mostly absorbed as an ionized form in the first part of the small intestine, but it can also be absorbed throughout the small intestine. This process of ionization requires an acidic environment to separate calcium from its salt or food complex. Healthy individuals have a stomach pH between 1 and 3 when fasting, which is an ideal environment for calcium to dissolve in (Busque *et al*., 2005).

In individuals with low stomach acid levels, the absorption of calcium carbonate, which is an insoluble form of calcium, is greatly hindered when consumed on an empty stomach. However, absorption of calcium citrate, which is a soluble form of calcium, remains unaffected (Palermo *et al*., 2019).

The release of calcium from food is dependent on the presence of stomach acid and the acidity of the proximal duodenum. This acidity allows for the absorption of calcium. Without this release, calcium is unable to be absorbed triggering compensatory mechanisms like secondary hyperparathyroidism. Parathyroid hormone activates a variety of compensatory mechanisms to recoup calcium malabsorption, one of which is to increase bone resorption and ultimately a reduced bone mass and a heightened risk of fractures (Insogna, 2009).

It is unclear how using PPIs leads to a higher risk of osteoporosis and bone fractures, however, there are a few potential explanations that have been proposed.

Furthermore, taking PPI medication for an extended period can decrease the body's capability to absorb vitamin B12, which can lead to various issues such as difficulty walking, muscle weakness, decline in cognitive function, and visual disturbances. This predisposes to a higher risk of falling, which may contribute to low trauma fractures, including hip fractures, in older individuals who do not have osteoporosis (O'Leary and Samman, 2010).

Therefore, some possible ways that PPIs can cause fractures include increased histamine secretion and increased activity of

the parathyroid gland caused by high levels of gastrin in the stomach, as well as decreased absorption of minerals and vitamin B due to low stomach acid levels. There is also some limited research suggesting the direct effects of PPIs on bone cells (Thong *et al*., 2019).

According to a study conducted by Shandookh *et al*. (2022), it was found that proton pump inhibitors have a significant impact on bone mineral density and are commonly linked to the development of osteoporosis and osteopenia in the lumbar spine. The research showed a significantly lower serum calcium, vitamin D, and inorganic phosphorus in PPI users compared to non-users, as well as an elevated level of alkaline phosphatase activity. The study also utilized Dual X-ray absorptiometry (DXA) scans, a two-dimensional technique that measures areal (mg/cm2) rather than volumetric (mg/cm3) BMD, and found that all scores, including T-scores, Z-scores, and total scores, were significantly lower in PPI users than non-users. The risk factors associated with decreased bone density among PPI users included a high body mass index, long-term and high-frequency use of PPIs

A comprehensive analysis of 32 observational studies revealed that individuals taking PPI have a higher risk of experiencing osteoporosis (HR:1.23; 95% CI:1.06-1.42), any-site fractures (HR: 1.30; 95% CI: 1.16-1.45), spine fractures (HR:1.49; 95% CI:1.31-1.68) and hip fractures (HR:1.22; 95% CI:1.15-1.31) as determined by a random model. However, no correlation was found between PPI use and a loss of BMD in the spine (SMD: −0.06; 95% CI: −0.54-0.41), or in the femoral (SMD: −0.27; 95% CI: −0.62-0.09). Additionally, the research showed that using esomeprazole and rabeprazole increases the risk of fractures and osteoporosis, but no such correlation was found for any other types of PPI (Liu *et al*., 2019).

A study of a large group of elderly Korean females reported that utilizing PPIs correlated with a higher risk of osteoporotic fractures in comparison to just using H2RA. This correlation remained consistent regardless of major risk factors for fractures. Specifically, the risk of fractures increased with PPI use for one year or more or recent PPI use, but it did not alter with a higher cumulative PPI dose. Further analysis of the fracture site also revealed that PPI use was associated with a higher risk of vertebral and hip fractures, but not other types of fractures (Park *et al*., 2020).

However, it is possible that the association discovered between PPI usage and bone disease could be a selection bias of, considering the fact that elderly individuals with osteoporosis and multiple health conditions causing limited mobility are often prescribed PPI (Liu *et al*., 2019).

The significance of this association in terms of medical treatment is uncertain due to the small odds ratios, lack of a clear correlation between dosage and effect, and the presence of other variables that may influence the results in many research studies. Despite this, a clear explanation for the causal link between using PPI medications and the risk of fractures has yet to be determined (Leontiadis and Moayyedi, 2014).

In a study involving postmenopausal women, there were minimal changes found in bone health after 26 weeks of taking either a placebo or two powerful acid-reducing medications, dexlansoprazole and esomeprazole. Although there were increases in bone turnover, both the formation and breakdown of bone increased equally. The study found no evidence that these medications had an impact on bone density, mineral levels in the blood and urine, levels of parathyroid hormone, or true fractional calcium absorption. This research strongly suggests that these medications do not affect calcium absorption or overall bone health and any potential link between these medications and fractures is not through the usual metabolic pathways that lead to fractures (Hansen *et al*., 2019).

Despite mixed findings on the impact of PPIs on bone mineral density, several systematic reviews have found a link between taking PPIs and a higher incidence of fractures (Aleraij *et al*., 2020).

CONCLUSION

There has been a growing concern in last years about the potential negative effects of prolonged intake of PPIs, which are commonly used medications that can be purchased without a prescription. Despite this, many patients continue to use PPIs without seeking medical guidance.

In recent years, there has been a lot of thought given to the potential negative side effects of using PPIs for extended periods of time, which has resulted in some warnings from agencies that monitor drug safety. However, for the majority of these side effects, the research is not strong or conflicting and, even though there may be a potential biological reason for the effects, it cannot be proven that they are directly caused by the use of PPIs.

Nevertheless, medical professionals should still advise patients to use the lowest possible dose of PPIs for the shortest amount of time to minimize potential side effects.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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