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LONG-TERM CONSEQUENCES OF PROTON PUMP INHIBITOR USAGE: ASSOCIATED RISKS

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Abstract

Since their release into the market in 1989, proton pump inhibitors (PPIs) have marked a before and after in the treatment of illnesses linked to stomach acid. Owing to a unique, extremely efficient method of action that prevents parietal cells from obstructing the last convergent stage of stomach acid production, as well as a small number of, generally manageable side effects. Due to their rapid efficacy in treating peptic ulcer disease, gastroesophageal ulcers, Zollinger-Ellison syndrome, nonsteroidal anti-inflammatory drug-associated ulcers, and the elimination of Helicobacter pylori, these drugs quickly replaced other pharmacological substances like H2 antagonists as the preferred treatment option. This has resulted in an exponential rise in their prescription up to this point. Nevertheless, there is growing evidence of long-term negative consequences from the frequent use of PPIs, including an increased risk of dementia, enteroendocrine cancers, liver, renal, and cardiovascular disease.

KEY WORDS: Proton pump inhibitors, Complications.

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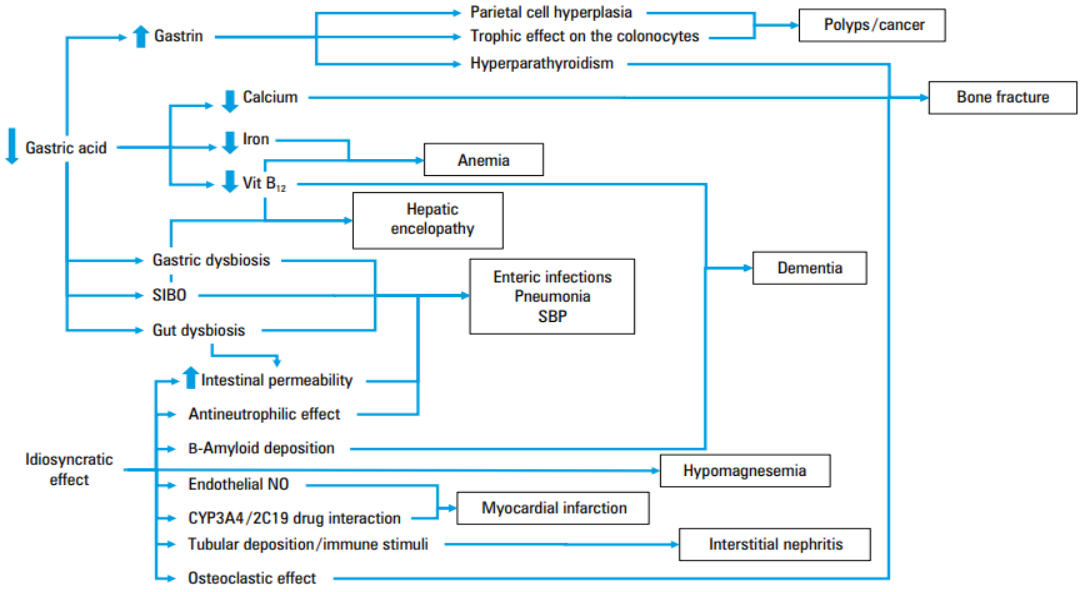
INTRODUCTION

The last stage of gastric acid production by parietal cells in the stomach is called H+/K+ adenosine triphosphatase (ATPase), and proton pump inhibitors (PPIs) are often used irreversible inhibitors of this enzyme [1]. As a result, they are frequently chosen as the treatment for illnesses caused by excess acid. The first medication in this family, omeprazole, was released in 1989. Lansoprazole, rabeprazole, pantoprazole, esomeprazole, and dexlansoprazole then followed (2009) [2]. As compared to older drugs like anticholinergics, synthetic prostaglandin analogues, and histamine2-receptor antagonists (H2RAs), PPIs have been shown to be more patient-tolerated, safer, and more effective in suppressing acid production [3-4]. Regarding the use of PPIs, there is rising concern. Omeprazole, esomeprazole, and lansoprazole are all accessible for over-the-counter purchasing in the India, increasing accessibility for the general public. Although over-the-counter PPIs are only authorised for the short-term treatment of persistent heartburn, they are frequently used to treat additional symptoms of the upper gastrointestinal tract, such as bloating, stomach discomfort, and burp [5]. According to current studies, PPIs should be taken for the shortest time feasible at the lowest effective dose because long-term usage may have complications [6] such as infections, decreased nutritional absorption, dementia, renal disease, and hypergastrinemia [7]. Given the growing concerns regarding PPI overuse in the general population, the purpose of this review is to discuss the complications associated with PPI usage.

(Figure: 1) Proton pump inhibitors, Dosage level and OTC in India

Drug	Dosage	Over-the-counter
Omeprazole	**10, 20, 40**	**Yes**
Esomeprazole	**20, 40**	**Yes**
Lansoprazole	**15, 30**	**No**
Dexlansoprazole	**30, 60**	**No**
Pantoprazole	**20, 40**	**Yes**
Rabeprazole	**20**	**Yes**

(Figure: 2) Complications of long-term and inappropriate using proton pump inhibitors



COMPLICATIONS IN PROTON PUMP INHIBITORS

Kidney diseases: Acute and chronic kidney damage have been related to the usage of proton pump inhibitors (PPIs). An uncommon but unusual side effect of PPIs on the kidneys is acute interstitial nephritis (AIN), a hypersensitivity reaction that causes inflammation of the renal blood fluids and tubules. The elderly may be more vulnerable to PPI-induced AIN, which may be mild and free of systemic allergy symptoms [8].

Since 1992, case reports have connected the use of PPIs with acute kidney damage (AKI), and more recently, two studies have connected the use of PPIs with an elevated risk of chronic kidney disease (CKD), which was not primarily attributed to the risk of AKI. Longer-term PPI users had a greater chance of developing CKD. More than half of patients who experienced PPI-induced acute interstitial nephritis (AIN) did not fully recover, indicating that PPI-induced CKD is likely caused by the progression of acute interstitial nephritis from inflammatory interstitial infiltrates and edema to chronic interstitial scarring and tubular atrophy [9].

Dementia: Proton pump inhibitors (PPIs) are frequently recommended to treat gastrointestinal conditions caused by excess acid. Concerns have been raised concerning their prolonged usage and the potential for dementia. Two scientific explanations for this relationship have been put forth: a vitamin B12 deficiency and higher amounts of beta-amyloid in the brain. Studies have linked vitamin B12 insufficiency to cognitive deterioration, and PPI use may lower vitamin B12 levels. PPIs may decrease stomach acid output, which may result in hypochlorhydria and compromise the absorption of vitamin B12 from dietary proteins [10].

PPIs may interact with brain enzymes and raise beta-amyloid levels, according to recent animal research. The precise process, nevertheless, is unknown. Physicians have yet to reach agreement on the relationship between PPI usage and dementia risk due to the contradicting data on the subject. The majority of PPI users who experience brain dysfunction do so as a result of chronic PPI medication [11]. Neurological adverse effects such headaches, vertigo, depression, and sleeplessness have been associated to PPIs like lansoprazole, esomeprazole, and pantoprazole. PPIs may have an impact on the ionic pumps that regulate the membrane potential in neurons, which might explain their neurological effects.

PPI users have lysosomes that are less acidic, which may hinder their capacity to break down amyloid-beta protein, the main material that builds up in the brains of people with Alzheimer's disease. Additional ideas include unintended consequences resulting from underlying conditions like magnesium and vitamin B12 deficiency [12].

Fracture risk: It is debatable if using proton pump inhibitors (PPIs) increases your risk of fracture. Among patients who also have osteoporosis risk factors, such as renal failure, certain retrospective studies reveal a dose-dependent association between PPIs and reduced bone mineral density, which increases the risk of fractures, particularly hip fractures. For PPI users to avoid osteoporotic fractures, routine osteoporosis prevention is advised. Recent prospective investigations, however, failed to detect any appreciable short- to medium-term changes in bone mineral density or fracture risk among PPI users [13].

The hypochlorhydria-induced malabsorption of calcium, gastrin-induced parathyroid hyperplasia, and prevention of bone resorption by inhibiting local H+/K+ ATPase are the suggested mechanisms associating long-term PPI usage with lower bone mineral density. Due to the usage of PPIs, vitamin B12 insufficiency may also result in homocysteinemia, which is associated with weaker bones. PPI-induced hypergastrinemia has been demonstrated in

animal models to cause parathyroid hyperplasia, which lowers femur bone density. Evidence does, however, point to the possibility that PPIs could prevent osteoclastic vacuolar proton pumps, which would diminish bone resorption [14-15]. Nevertheless, compared to oral delivery, a substantially larger dosage is needed for this action. Hence, it is doubtful that the impact on osteoclastic proton pumps will have any physiologically relevant effects.

Cardiovascular disease: PPIs, which are frequently prescribed medications, have a history of having negative effects on the cardiovascular system. They could prevent clopidogrel from being activated, which would raise the risk of clot formation in those with acute coronary syndrome [16]. Moreover, PPIs can lower the amounts of nitrous oxide in the endothelium by preventing the action of nitrous oxide synthase, which in turn inhibits dimethylarginine dimethylaminohydrolase. Particularly in individuals who have been receiving prolonged or high-dose PPI therapy, this decline in nitrous oxide may contribute to the increased risk of serious acute cardiovascular events such acute myocardial infarction and stroke [17]. Hypomagnesemia, which can extend the QT interval and possibly result in dangerous ventricular arrhythmias, has also been linked to PPI use.

Chromogranin A, an essential marker of neuroendocrine tumours and a putative biomarker of cardiovascular disease, may also be elevated in the blood as a result of PPI use [18]. Vasodilatory and cardioregulatory actions of chromogranin A and its related peptides may be short-term adaptive but long-term detrimental. Lastly, PPIs may reduce the antiplatelet action of clopidogrel by out-competing the cytochrome P450 isoenzyme CYP2C19 [19]. The possible negative effects of PPIs on cardiovascular health should be taken into account when prescribing these medications, even if the majority of the data for these relationships is restricted to ex vivo research.

Liver (Hepatic encephalopathy): PPIs have been linked to a higher incidence of cirrhosis-related complications such liver cancer, hepatic encephalopathy, and spontaneous bacterial peritonitis [20]. Patients who have been using PPIs for more than a year had a twice-increased risk of developing hepatocellular carcinoma compared to those who have had less than a year of follow-up, suggesting that the risk may be associated to chronic PPI usage. It is not fully understood how PPI usage causes liver damage, but one theory suggests that it may be due to changing intestine microbial composition [21], which raises the amounts of potentially hazardous chemicals such secondary bile acids in the portal venous system.

Due to the drug's metabolism in the liver, which might result in hypergastrinemia-induced carcinogenic effects, especially on liver cells, patients with liver illness may be at an elevated risk for hepatotoxicity from PPI usage. PPI usage may also lower vitamin B12 levels due to decreased stomach acidity or modify the gut microbiome, which both contribute to an increased risk of hepatic encephalopathy [22]. Last but not least, cultured human liver cells exposed to PPIs exhibited gene expression in the liver that was comparable to well-known carcinogens, indicating a potential connection between PPI usage and liver cancer. Our results underline the need for caution when prescribing PPIs, especially to patients with liver illness, and the need of monitoring for potential side effects of long-term usage.

Respiratory infection [Pneumonia]: By encouraging bacterial growth in the stomach and interfering with neutrophil function, PPIs may raise the risk of pneumonia [23]. This discovery, however, is only supported by in vitro investigations, and its applicability is debatable. Observational studies have linked PPI usage to an elevated risk of community-

acquired pneumonia (CAP) [24]; however, this risk is mostly felt by people who have just started using PPIs as opposed to people who have been taking them for a while. Among patients randomly assigned to PPIs or a placebo for ulcer prevention, the OBERON research discovered comparable incidence of pneumonia [25]. A manufacturer-sponsored investigation of short-term RCTs likewise revealed no conclusive evidence of a link between PPIs and pneumonia.

Gastrointestinal infection [Colon]: The use of PPIs has been associated with an increased risk of incidental and recurrent Clostridium difficile infections as well as other enteric infections [26-27]. This is due to the important role of acid secretion by parietal cells in the gastrointestinal tract, which provides an immunological barrier. When PPIs inhibit gastric acid secretion, hypochlorhydria can occur, increasing the risk of bacterial colonization and susceptibility to enteric infections.

Studies suggest that more than two-thirds of inpatient prescriptions for acid suppression are not medically necessary, and tens of thousands of cases of Clostridium difficile infection occur annually in the India [28]. Although it was previously believed that PPIs could change the normal intestinal flora and contribute to the development of these infections, recent research has challenged this hypothesis. Additionally, PPIs have been linked to microscopic colitis, but the underlying mechanisms remain unclear.

Muscle [Myopathy]: The co-administration of a PPI with a non-steroidal anti-inflammatory drug or statin has been known to cause myopathy, including rhabdomyolysis [29-30]. This is thought to occur because PPIs can inhibit the metabolism of statins, which are usually metabolized by the CYP3A4 enzyme. This inhibition can lead to dose-related adverse effects, including myopathy.

Gastrointestinal malignancies: PPIs are drugs that decrease the amount of acid produced in the stomach. However, they can cause an increase in the hormone gastrin, which can lead to the growth of certain cells and the development of tumours in the gastrointestinal tract [31]. PPIs can also make it easier for Helicobacter pylori, a bacterium that can cause stomach ulcers, to grow in the stomach.

Some studies have suggested that PPIs may increase the risk of developing cancer in the gastrointestinal tract, while others have not found a link between the two. Specifically, studies looking at the relationship between PPIs and colorectal cancer have not found any conclusive evidence to support a link between the two [32]. Although there is some mixed evidence, any increased risk of developing tumours in the gastrointestinal tract from taking PPIs is likely to be very small.

Blood [Anaemia]: When patients take PPIs, their risk of developing anaemia increases due to a decrease in gastric acidity. This reduced acidity can make it harder for the body to absorb important nutrients like iron and vitamin B12. When the pH level in the stomach is higher than 3, ferric ions are not as easily reduced to ferrous ions, which can lead to lower absorption of iron. Vitamin B12 is also affected because it is normally released by hydrochloric acid and pepsin in the stomach, but PPIs can reduce this acidity and interfere with the absorption process. This can lead to a deficiency of B12, which can contribute to anaemia.

Micronutrient Deficiencies: Numerous studies have explored whether low levels of stomach acid caused by PPIs can lead to significant micronutrient deficiencies, which can affect the absorption of minerals such as calcium, iron, and magnesium, as well as protein-bound vitamin B12 in the diet.

Calcium: In terms of calcium absorption, while deep acid suppression may interfere with it, this effect doesn't apply to water-soluble calcium salts or those found in milk

or cheese [33]. Additionally, if water-insoluble calcium is taken with a slightly acidic meal, malabsorption in the case of achlorhydria can be fully reversed.

Iron: There is limited research on the potential link between PPIs and iron deficiency, but long-term use in patients with hereditary hemochromatosis has been associated with reduced absorption of non-heme iron in the short-term and decreased annual phlebotomy requirements in the long-term [34].

Magnesemia: Although cases of severe hypomagnesemia have been reported in patients on chronic PPI therapy, they appear to be infrequent and may be an idiosyncratic reaction. However, observational studies suggest a modest positive correlation between PPI use and hypomagnesemia [35].

Vitamin B12: Multiple studies have investigated the relationship between long-term PPI use and the risk of vitamin B12 deficiency, and most have reported a 2-4 times higher risk of deficiency associated with PPI therapy, but some studies have not found any such association [36].

Stomach [Fundic gland polyps]: The suppression of acid is believed to cause an increase in the number of parietal cells, which can result in changes in tissue structure and the formation of multiple polyps [37]. The use of PPIs may also make it more likely for fundic gland cysts to develop, and can lead to a build-up of mucus in the fundic pits due to a decrease in the secretion flow of the glands.

CONCLUSION:

In conclusion, proton pump inhibitors (PPIs) have revolutionized the treatment of gastric acid-related diseases since their introduction in 1989. They are highly effective and have generally manageable side effects. However, there is growing concern about their long-term use and the potential complications associated with it. The increased accessibility of over-the-counter PPIs has also contributed to their overuse in the general population. Complications associated with PPI usage include an increased risk of dementia, enter-endocrine cancers, liver, renal, and cardiovascular disease. Physicians should be cautious in prescribing PPIs and advise their patients to use them for the shortest time possible at the lowest effective dose. Further studies are needed to fully understand the risks and benefits of PPI usage.

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