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Potential Risks and Drawbacks of Long-Term Proton Pump Inhibitors Use

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Abstract **Review Article**

In today's world, proton pump inhibitors (PPIs) are one of the most commonly prescribed pharmacological types. Many gastrointestinal diseases such as gastroesophageal reflux or Barrett's esophagus, as well as laryngopharyngeal reflux, may benefit from these. However, numerous studies have been published that link PPIs to a variety of dangers and problems, including bone fractures, infection, myocardial infarction, renal illness, and dementia. By examining key articles and addressing the debates around those findings, this review exposes several of these potential negative side effects. To provide proper counseling of their patients, the diligent otolaryngologist should be aware of the current status of the literature and the hazards associated with prescribing PPIs. PPIs must be prescribed correctly in order to optimize outcomes and reduce risks and costs to the healthcare system. Overuse and misuse of PPIs, on the other hand, raises the risk of side effects. Because most gastric-acid-related illnesses necessitate long-term treatment, patients taking additional drugs in addition to a PPI are likely to experience clinically significant adverse drug interactions. Clinicians must only administer PPIs when they are proved to be required.

Keywords: PPIs, adverse effects, overuse, misuse, side effects.

INTRODUCTION

Proton pump inhibitors (PPIs) are those drugs that are commonly prescribed all over the world. Patients with gastroesophageal reflux, peptic ulcer disease, Helicobacter pylori infection, and Barrett's esophagus are treated with these drugs. PPI use in adults has been repeated since 1989, from 3.9% in 1999 to 7.8% in 2012. The FDA has approved six PPIs: Omeprazole, Lansoprazole, Dexlansoprazole, Esomeprazole, Pantoprazole, and Rabeprazole. Over-the-counter kind of Omeprazole, Esomeprazole, and Lansoprazole are currently available. As a result, it is one of the most commonly prescribed medications to the high rate of gastrointestinal disorders such as gastroesophageal reflux disease and peptic ulcers being diagnosed. Considering the PPIs released on the market, Different types of pharmaceuticals can be found in the market. In the family of PPIs, it is possible to distinguish distinct molecules that have the same potential to reduce stomach acid secretion, based on the latest releases on the pharmaceutical market. PPIs work by inhibiting the hydrogen/potassium adenosine triphosphatase enzyme system of the gastric parietal cells (the H + /K + ATPase or gastric proton pump), which allows H+ ions to be secreted into the gastric lumen. PPIs are administered in an inactive, lipophilic form that crosses cell membranes to reach the cytoplasm. In an acidic environment, the inactive drug is protonated and rearranges into its active form, binding covalently and irreversibly to the gastric proton pump and deactivating it. The proton pump represents an ideal target for inhibiting acid secretion. Since the first PPI, omeprazole, was launched in the late 1980s, the use of PPIs has skyrocketed. In a study conducted in the United States, it was discovered that PPIs were utilized in 4% of ambulatory care visits in 2002 and 9.2% of visits in 2009 (p 0.001). It's worth noting that 46.7% of PPI patients were 65 or older, which is a considerable number given that there were 919 patients. In 2009, there were over a million ambulatory visits. Furthermore, the majority of cases revealed questionable PPI use, with 62.9% of patients having no recorded gastrointestinal problems, diagnoses, or

concurrent high-risk drugs justifying PPI use. Long-term PPI use, defined as three or more PPI prescriptions filled in one year, was discovered in one out of every nine older persons in one research that was done at Sweden in 2010. In addition, roughly 40% of long-term PPI users who were older adults had no indication for their usage. Overall, the usage of PPIs has increased over the world, and it's especially alarming that so many people are taking them when they don't need to. According to current evidence, PPIs are frequently overprescribed, with 25-70% of prescriptions having no valid rationale. PPIs account for more than $10 billion in healthcare costs in the United States (US), with global costs exceeding $25 billion per year. Regardless of the US Food and Drug Administration's restricted approval, clinicians can legally prescribe drugs based on their own interpretation of scientific data or clinical judgment (FDA). Off-label pharmaceutical use is common in intensive care units, with PPIs accounting for the most off-label use (up to 55%). Even drugs with a relatively benign profile might have long-term detrimental, unintended repercussions due to extensive and often open-ended use. The overtreatment of functional dyspepsia, as well as the prevention of gastroduodenal ulcers in low-risk patients, low-dose steroid therapy without additional risk factors, and systemic anticoagulation without additional risk factors for gastroduodenal injury, are some of the most common inappropriate uses of PPIs. The Food and Drug Administration (FDA) in the United States and the National Institute for Clinical Excellence in the United Kingdom have produced guidelines on the indications for PPIs (particularly in hospitalized patients) that are commonly prescribed. Erosive eczema was one of the main symptoms. NSAIDs, esophagitis, dyspepsia caused by non-steroidal anti-inflammatory drugs (NSAIDSs) and its consequences, critically ill patients requiring mechanical ventilation, and H. pylori treatment in humans. Antibiotics should be used in tandem. PPIs are frequently prescribed as an empiric therapy for LPR symptoms by primary care doctors and otolaryngologists, with varying degrees of success. This empiric medication can be used as a diagnostic tool in some circumstances. Apart from the financial cost of PPI use in the general population, questions about its use and potential side effects like bone fractures, dementia, cardiac events, renal illness, and infection continue to appear. As the number of stories and media coverage related to epidemiology research looking at the risk of PPIs grows, otolaryngology outpatient clinics are discussing their possible concerns on a weekly, if not daily, basis. The goal of this study is to summarize the potential dangers of using PPIs as a decision-making tool and for patient counseling. Overexposure to or extended use of a proton pump inhibitor has lately been linked to an increased risk of infection by the deadly bacteria Clostridium Difficile, according to the US Food and Drug Administration (FDA) [1-8].

Table 1: Generic PPI along with their FDA approved indications

FDA Approved Indications	Pantoprazole	Omeprazole	Rabeprazole	Esomeprazole	Lansoprazole
Short term treatment of active gastric ulcers		√			√
Short term treatment of active duodenal ulcer		√	√		√
Symptomatic gastroesophageal reflux disease	√	√	√	√	√
Healing of NSAIDS associated gastric ulcers	√	√	√	√	√
Healing and maintenance of erosive esophagitis	√	√	√	√	√
H. pylori eradication with antibiotic combination		√	√	√	√
Zollinger-ellison syndrome	√	√	√	√	√
Risk reduction of NSAIDS associated gastric ulcer				√	√

Potential Adverse Effects of PPIs Use:

1. Bone Density Loss and Fracture Risk

Although the specific mechanism by which PPIs cause bone fracture is unknown, two theories include interfering with calcium salt absorption and inhibiting bone remodeling. Hypochlorhydria may interfere with calcium salt absorption, resulting to secondary hyperparathyroidism and subsequent bone resorption to maintain calcium levels, according to the first hypothesis. However, several investigations have found that acid suppression has little effect on calcium absorption. The second hypothesis posits that a direct blockage of the bone specific proton pump associated with osteoclasts causes bone remodeling to be disrupted, resulting in increased bone fragility without a change in bone mineral density. With age, the morbidity associated with fractures, particularly hip fractures, can be exceedingly catastrophic. One of the studies found an elevated risk of hip fracture in a 2016 meta-analysis of 15 case control and cohort studies on bone fractures linked with the use of PPIs. These results, however, were linked to heterogeneity across studies. In addition, the risk of any site fracture increased as did the risk of spine fractures in this sub-analysis. The authors also

showed that the risk remained when treatment duration was divided into subgroups of less than or more than one year. This significant increase in hip fracture was sustained in a sub-analysis limited to cohort studies. Despite these legitimate concerns, five major longitudinal studies published since 2008 have failed to show a meaningful change in BMD (as measured by T score) as a result of PPI usage. The SWAN trial found no change in yearly BMDs between patients who started taking PPIs versus those who started taking a histamine type 2 receptor antagonists in a cohort of women with a median follow-up of 9.9 years (H2RA). When comparing PPI users to nonusers, a study observed no difference in BMD. They did discover, however, that those who use PPIs have lower baseline total hip and femoral neck BMD. One of the profound studies showed that baseline hip bone density was lower in male PPI users than nonusers in a third trial. Given the absence of evidence for a link between BMD and pathologic fracture with PPIs, and the fact that the majority of studies found no change in BMD with these drugs, there is inadequate evidence to propose routine BMD monitoring or calcium supplementation in PPI patients [9-19].

2. Hypomagnesaemia

Magnesium shortage has been related to both cardiovascular and non-cardiovascular mortality due to its importance as an electrolyte in the body. Arrhythmias, muscular weakness, tetany, and convulsions are only a few of the side symptoms of severe hypomagnesaemia. Because of interaction with the Melastatin 6 (TRMP6) and TRMP7 active transporters, hypomagnesaemia is most likely caused by increased renal loss and decreased absorption in the gastrointestinal tract with PPI usage. Three cohort studies, five cross-sectional studies, and a case control study on hypomagnesaemia linked to PPI usage were included in their meta-analysis. Cheungpasitporn *et al*., found a pooled relative risk (RR) of 1.43, which increased to 1.63 when only studies with high GRADE criterion scores were included. In both studies, there was a lot of heterogeneity in the data. Although this study suggests a link between PPI usage and hypomagnesaemia, it is unclear whether this was linked to higher morbidity [20].

3. Iron Deficiency

Because stomach acid transforms dietary iron from ferric to ferrous form, acid suppression with PPIs or H2RA may result in malabsorption. Iron deficiency, if left untreated, can lead to anaemia, asthenia, and other problems. The Kaiser Permanente Northern California (KPNC) health system found an enhanced link between iron deficiency and PPIs in a case-control study. They found that a two-year or longer course of PPIs was associated with an attributable risk (AR) of 48 to 71 incident cases per 1000 patient years. With a higher daily dose and a longer time of ingestion, the link was much stronger. H2RA use was also linked to an increased risk [21].

4. Vitamin B12 Deficiency

When the body lacks vitamin B12, it is called B12 deficiency. PPIs and H2RAs can cause vitamin B12 malabsorption by inhibiting vitamin B12 cleavage from dietary proteins. If left untreated, vitamin B12 deficiency can result in anaemia and neurological problems. With two or more years of PPI use prior to the index date, one of the most significant studies to show a link between PPI use and vitamin B12 deficiency discovered a significantly increased risk of this vitamin deficiency. This risk increased as daily intake increased and decreased as use was discontinued. H2RA showed the same link, but to a lesser degree. This finding is supported by other smaller studies while another study showed no such link [22-25].

5. Community-Acquired Pneumonia

Community-Acquired Pneumonia (CAP) is a type of pneumonia that occurs in those who have been exposed to it in Lambert *et al*., found a pooled risk of CAP of 1.49 with ambulatory PPI medication in a systematic evaluation of 26 papers looking at acid suppression and the risk of CAP. During the first month of treatment, the combined risk increased to 1.61. This first increase in risk was attributed by the authors to the micro biome's peak flux period. PPIs may be recommended for early symptoms of undetected pneumonia (protopathic bias), or PPI prescriptions may be related with unmeasured confounding events, according to Freedberg *et al*., (e.g., stress, hospitalizations). As a result, the degree and direction of these biases may affect the pooled effect, making it difficult to interpret these primarily observational studies. Lambert *et al*., also found that just 4 of the 26 papers they looked at were randomised control trials (RCTs). In the largest of these trials, the experimental and control groups with CAP experienced equal rates of adverse events. In a recent meta-analysis, Eom *et al*., found no evidence of an increased risk of pneumonia in high quality RCTs [19, 26-28].

6. Salmonella and Campylobacter Infections

The colonisation of the foregut by intestinal bacteria and hypochlorhydria has been linked. For S. paratyphi and S. enteritis, a pH of less than 3.0 is bactericidal, whereas a pH of more than 4.0 has no effect on bacterial colonies. PPI use was linked to an elevated risk of salmonella infection by 4.2–8.3 in observational studies. Bavishi *et al*., found an increase in Campylobacter infections in individuals on PPI therapy in a systematic evaluation of enteric infections with PPI use (RR 3.5–11.7). PPI use in gastroenteritis has a risk ratio of 2.9 in larger case control studies [29-31].

7. C. Difficile Infections

PPI use has also been linked to C. Difficile infections acquired in hospitals. In vitro, the vegetative state and spores of C. Difficile were found to be stable at pH > 5, validating the indicated elevated risk. Tleyjeh *et al*., found a 1.51 adjusted pooled RR for C. Difficile infection in a systematic evaluation of 37 case control studies and 14 cohort studies. However, the GRADE standards graded the evidence in their review as "extremely low quality," and the number needed to harm (NNH) was 3935 (AR 0.25/1000 patient years), compared to a NNH of 50 for patients who finished 2 weeks of antibiotics [30, 32].

8. Kidney Disease

Since an initial 1992 report on a case of acute tubular necrosis after PPI usage, acute kidney illness has been thought to be a risk of PPI use. PPI medication was connected to acute and chronic kidney disease as well as progression from chronic kidney disease to end-stage renal disease in two major observational studies published in 2016. To analyse the risk of acute and chronic kidney illness associated with PPI usage, Lazarus *et al*., looked at two study populations and health system–wide data from the Geisinger Health System. With 248,751 patients, 16,900 of whom were on PPIs, the second dataset contained 20 times the population. A propensity score matching hazard ratio (HR) of 1.29 for acute renal disease and 1.16 for chronic kidney disease were found in the broader population. PPI use also raised HRs for the existence of indicators for chronic kidney disease development, such as a doubling of serum creatinine, a >30% fall in eGFR, and progression to end-stage renal disease. Both investigations established a link between PPI usage and chronic kidney disease using propensity score matched HR, which took into consideration confounding comorbidities and known covariate exposures. However, no evidence from RCTs has yet been produced to substantiate causation and establish this link [33-35].

9. Myocardial Infarction

Proton pump inhibitors have been linked to myocardial infarction (MI) and acute cardiac events through two different pathways. PPIs can directly raise vascular resistance by blocking nitric oxide synthase activity, and they can compete with P450 isoenzyme activation of clopidogrel in the liver. Ex vivo studies demonstrate that PPIs, particularly omeprazole, block the liver P450 isoenzyme CYP2C19, which is necessary for the formation of the active clopidogrel metabolite. In 2009, the FDA issued a black box warning for the combined use of clopidogrel and omeprazole based on this ex vivo findings and other observational studies. Bhatt *et al*., found no differences between the groups in adverse cardiac events, defined as death from cardiovascular causes, acute nonfatal myocardial infarction, need for revascularization, and acute stroke, one year later in an RCT that compared patients taking clopidogrel and omeprazole versus clopidogrel and placebo. The risk of an adverse cardiac event in the general population was assessed in two community-based observational studies. Shah *et al*., used a novel population-based data mining algorithm to look at the MI relationship in patients diagnosed with GERD in another population-based study. PPI use was associated with an OR of MI 1.16 in this population-based observational analysis. H2RA was employed as a control in both of these large population-based investigations, with no substantial risk of adverse cardiac events associated with H2RA exposure [36, 37].

10. Dementia

There have been two ideas presented for the development of dementia associated with the use of PPIs. Low levels of the protective vitamin B12 or direct suppression of the enzymatic clearance of amyloid, as proven in mouse models, are among these ideas. Concerns concerning PPIs and dementia arose when a population-based observational cohort research in Germany looked at the occurrence of dementia in approximately 74,000 adults over 75 years old. Prior to diagnosis, PPIs were used for an 18-month period, separated into three 3-month blocks. A patient's regular PPI use was defined as receiving at least one PPI prescription in each of the six 3-month blocks. The adjusted HRs of acquiring dementia were 1.44 with regular PPI usage and 1.16 with intermittent use (i.e., 1–5 of the 3-month blocks with at least one PPI prescription) when compared to the general population. There have been questions raised concerning the accuracy of these conclusions. The kind of dementia, degree of education, and impact of polypharmacy could not be determined from this data set, according to the investigators. Furthermore, PPI users were linked to all a priori variables, implying that they were less healthy than the rest of the German population. Despite the fact that the authors controlled for these covariates in their analysis, the severity of these comorbidities was not taken into account, and additional potential uncaptured or unexplained covariates cast doubt on the study's findings. Following research that looked at dementia and PPIs brought Gomm *et al*., findings into doubt even more. Goldstein *et al*., studied the development of moderate cognitive impairment and progression to Alzheimer's disease in a prospective cohort of 10,486 participants in the National Alzheimer's Coordinating Centre Database, which included 2800 PPI users. PPI use at every follow-up interview (referred to as "always PPI use") was linked to a decreased risk of moderate cognitive impairment or dementia due to any cause. There was no link between "always PPI use" status and probable Alzheimer's disease cases. In addition, there was no link between intermittent PPI usage and mild cognitive impairment or dementia of any kind [38-43].

Relationships between Demographic Factors and Overuse of PPIs:

There is no link between overuse and demographic factors like age, gender, education level,

or place of residence. PPIs are widely overused throughout the world, and this overuse is not limited to a particular area, age group, or socioeconomic status. Interestingly, one of research found that physicians prescribed PPIs in 89.2% of cases, but 71% of those prescriptions were incorrect, even among gastroenterologists. A study conducted in China found that medical workers in China lacked sufficient understanding about the proper use of PPIs. Similar studies data were not available in India but such studies are needed to be carried out in India because medical staff's lack of awareness could be seen as a possible threat [43].

According to various research, PPIs are abused in hospital and ambulatory care settings. The appropriateness of PPI prescriptions is as low as 19% in some hospitals. Several variables should be examined before prescribing a proton pump inhibitor, including:

i. Dosages, therapy duration, and clinical grounds for utilizing a PPI, as well as a determination of the treatment's appropriateness;
ii. Is it necessary to employ H2-receptor antagonists before commencing a proton pump inhibitor; and
iii. Patients using a proton pump inhibitor for gastro-esophageal reflux disease (GERD) were also polled on how often they received one [44, 45].

With these considerations in mind, several clinical studies conducted in the hospital setting frequently conclude that the percentage of patients admitted to a hospital for gastrointestinal disorders who are already taking a PPI is significantly lower than the percentage that are prescribed a PPI upon discharge. According to a cross-sectional, prescription-based drug-utilization study conducted in Spain, 28.65% of 328 patients in a single hospital were prescribed a PPI at admission, 82.62% during their stay, and 54.75% at discharge, with improper indications for PPI prescription accounting for 74.47%, 61.25%, and 80.24%, respectively. Other studies have found that a considerable percentage of patients who were administered a proton pump inhibitor, either during their hospital stay or after release, did not follow the guidelines [44-49].

Academic and non-academic hospitals were included in a recent study conducted in Maryland. The FDA guidelines were used to investigate the compliance of all PPI prescriptions supplied at the hospitals. Study reveals that GI prophylaxis for low-risk patients is the most common reason for proton pump inhibitor prescription non-compliance, accounting for 82% of all non-compliant prescriptions. If proton pump inhibitors are given inappropriately, they can have substantial side effects, especially if a follow-up examination is not performed. A combination drug containing both Naproxen and esomeprazole was recently launched in the United States. This is because if a medicine contains both a PPI and an NSAIDS, the PPI will counteract any gastrointestinal side effects caused by the NSAIDS. While combining products may appear to be a good idea, it just increases the risk of proton pump inhibitor overexposure in the general population. As previously indicated, a proton pump inhibitor should only be taken when all other acid suppression drugs have failed. Long-term use of PPIs, or the use of a PPI in combination with a variety of other medicines, can have severe and, in some cases, fatal side effects if left untreated [44].

Side Effects of PPIs:

The majority of drugs have a long range of side effects that are mild to moderate. Headache, dizziness, diarrhoea, exhaustion, abdominal pain, nausea, dry mouth, and other side effects may occur, with the severity varying depending on the individual's susceptibility. Although many people may not notice them, they are not uncommon. As a result, when it comes to avoiding harmful consequences, it's critical to utilise drugs responsibly. Because proton pump inhibitors reduce stomach acidity, the most serious side effect of prolonged acid suppression is hypergastrinemia. Patients on a PPI are more likely to have ingested germs colonize their intestines, which can lead to bacterial gastroenteritis. Overexposure to or extended use of a proton pump inhibitor has recently been linked to an increased risk of infection by the lethal bacteria Clostridium Difficile, according to the US Food and Drug Administration (FDA). Long-term gastric acid suppression, hypergastrinemia, and neuroendocrine cell hyperplasia have all been linked to the creation of carcinogenic chemicals, according to evidence. Endoscopy can often obscure symptoms that are associated to the development of stomach cancer. Plasma gastrin levels should be examined in those people who are prescribed a proton pump inhibitor for a long time. Because proton pump inhibitors are typically recommended to control and avoid symptoms of a chronic gastrointestinal condition, treatment may last longer than four years. Calcium absorption in the small intestine is thought to be hindered by this extended therapy. Because proton pump inhibitors produce an elevation in gastric pH, calcium salts become insoluble and cannot be absorbed. In people who take a PPI, this reduction of calcium absorption is linked to osteoporotic fractures [45, 50-52].

Table 2: Side Effects of PPIs Use

S. No	Body Organ	Side Effect
1.	Respiratory	Nosocomial Pneumonia
2.	Kidney	Acute interstitial nephritis Chronic kidney disease
3.	Liver	Hepatocellular carcinoma
4.	Musculoskeletal	Osteoporosis Myopathy
5.	Blood diseases	Vit. B12 deficiency Iron deficiency Hypomagnesaemia Calcium deficiency
6.	Central nervous system	Dementia Hepatic encephalopathy
7.	Cardiovascular	Stoke Myocardial infection
8.	Gastrointestinal	Abdominal pain Nausea, vomiting
9.	Infections	C. Difficile Non-typhoid Salmonella Spontaneous bacterial peritonitis

Economic Effects of PPIs Overuse:

Proton pump inhibitors are frequently administered and overused in the absence of established therapeutic reasons. This erroneous use comes at a high price that adds up quickly over time. If the rate at which non-FDA compliant medications are supplied could be reduced, the government and the general public would save a significant amount of money. A retrospective cohort cost analysis was conducted in Michigan in a specific ambulatory care setting to put the extent of the economic effect of proton pump inhibitor usage into context. The entire cost of incorrect PPI usage in a year, whether it be non-compliant indication or inappropriate documentation, was $233,994 based on over-the-counter expenses and $1,566,252 based on average whole selling price expenditures, according to those engaged in the study. Another clinical trial that looked at the financial impact of abuse of proton pump inhibitors in non-ICU patients indicated that if measures were put in place to stop non-compliant administration of PPIs, an annual cost savings of over $35,000 may be realized [49, 51, 53].

Best Practices for PPIs Use:

i. Patients with GERD with acid-related complications (erosive esophagitis or peptic stricture) should use a PPI for at least 12 weeks to heal the esophagitis and up to 48 weeks to control symptoms. PPIs are highly effective in healing esophagitis and reducing GERD symptoms, and the advantages are likely to outweigh the risks. There is also strong evidence that patient with acid-related problems such peptic stricture benefit from ongoing PPI treatment.

ii. Patients with simple GERD, including NERD, who react to PPIs for a short period of time (less than 6 weeks), should try to quit or reduce their use. Patients who are unable to reduce their PPIs should be referred for tests to assist identify GERD from a functional syndrome. Short-term PPIs are quite successful in treating simple GERD. Most patients with simple GERD respond to short-term PPIs and can thereafter lower their PPI dosage to less than once a day. We would consider testing for an acid-related illness in this case because patients who cannot discontinue PPIs risk lifelong medication. Patients who do not respond to PPIs are frequently found to be free of GERD.

iii. Patients with unusual GERD symptoms, such as non-cardiac chest discomfort, may be given a 2-week trial of a proton pump inhibitor (PPI). If they don't reply, they should be checked to see if they're suffering from GERD-related chest pain. The majority of occurrences of non-cardiac chest pain could be caused by reflux or oesophageal motility problems. Differentiation is aided by a PPI experiment.

iv. Patients with Barrett's oesophagus should take a PPI for the rest of their lives. PPIs offer a definite clinical benefit and may help delay the progression of Barrett's disease. Long-term PPIs are anticipated to provide a net benefit in these patients.

v. Patients who are at high risk of ulcer bleeding from NSAIDSs, such as aspirin, should continue to take a PPI if they are on NSAIDSs. PPIs are particularly successful in avoiding ulcer-related bleeding in individuals who take NSAIDSs, such as aspirin, in correctly selected patients.

vi. Long-term PPI doses should be re-evaluated on a regular basis to ensure that the lowest effective PPI dose is recommended to treat the condition. Long-term PPI users frequently obtain higher-than-necessary PPI doses to control their illness. Because PPI reduction is frequently successful, it is logical to re-evaluate PPI medication on a regular basis to ensure that the minimal essential dose is administered.

vii. Probiotics should not be used to prevent infection in people who have been taking PPIs for a long time. Probiotics have not been shown to prevent infections in long-term PPI users.

viii. Long-term PPI users should not have their bone mineral density, magnesium, or vitamin B12 levels routinely checked or monitored. For people with any clinical characteristics suggestive of or in the presence of other risk factors for magnesium or B12 insufficiency or osteoporosis, a low threshold for testing should be maintained. For patients receiving long-term PPIs, there is no evidence for or against dedicated testing. Such testing (for example, for iron or vitamin B12 insufficiency) has not been shown to be beneficial.

ix. Patients on long-term PPIs should not have their blood creatinine levels routinely (yearly) evaluated unless there are additional reasons for renal surveillance. PPIs have a tiny idiosyncratic risk of renal toxicity such as AIN, according to the current literature. For the great majority of users, the current data does not support routine monitoring.

x. PPI formulations should not be chosen solely on the basis of potential concerns. There isn't enough evidence to rank PPI formulations according to risk.

xi. Patients with dyspepsia who have a lot of acid-related symptoms (epigastric pain syndrome) should take a PPI for a short period of time. In these patients, there is likely to be a net benefit with short-term PPIs [43].

CONCLUSION

Finally, it is obvious that PPIs are now being abused and misapplied. While all of the studies cited were conducted in the United States or other European countries, the conclusions reached in this article are universally applicable, as in a developing country like India, where over 500 branded PPI formulations are available, and the likelihood of misuse and abuse increases exponentially. PPIs, despite being a safe and effective class of medication, should only be taken when there is documented evidence of a GI illness that cannot be treated with an H2-receptor antagonist and when the use of a PPI is clinically justified. Increased clinician awareness of the proper use of PPIs will result in better patient outcomes at a reduced cost. Despite the fact that PPIs have been linked to a variety of negative side effects, there is little high-quality research on the subject, and negative side effects are still uncommon. Nonetheless, these allegations are alarming and should be taken into account in our decision-making process. As additional study is needed, the focus should be on appropriate diagnosis and careful administration of this medicine when it is indicated in the meantime. Alternative medical or surgical therapy should be considered if treatment is required for an extended period of time. The cautious otolaryngologist should be aware of those potential hazards and correctly balance the benefits of PPI use with the symptoms and comorbidities of their patients.

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