Review Article

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Adverse Effects Associated with Long-Term Use of Proton Pump Inhibitors

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Proton Pump Inhibitors are used widely to manage many gastric acid-related conditions such as gastroesophageal disease, gastritis, esophagitis, Barrett's esophagus, Zollinger-Ellison syndrome, peptic ulcer disease, nonsteroidal anti-inflammatory drug-associated ulcers, and *Helicobacter pylori* eradication, around the globe. This review article focuses on adverse effects associated with the long-term use of proton pump inhibitors. Various observational studies, clinical trials, and meta-analyses have established the adverse effects associated with the long-term use of proton pump inhibitors including renal disorders (acute interstitial nephritis, acute kidney injury, chronic kidney disease, and end-stage renal disease), cardiovascular risks (major adverse cardiovascular events, myocardial infarction, stent thrombosis, and stroke), fractures, infections (*Clostridium difficile* infection, community-acquired pneumonia, and Coronavirus disease 2019), micronutrient deficiencies (hypomagnesemia, anemia, vitamin B12 deficiency, hypocalcemia, hypokalemia), hypergastrinemia, cancers (gastric cancer, pancreatic cancer, colorectal cancer, hepatic cancer), hepatic encephalopathy, and dementia. Clinicians including prescribers and pharmacists should be aware of the adverse effects of taking proton pump inhibitors for an extended period of time. In addition, the patients taking proton pump inhibitors for long-term should be monitored for the listed adverse effects. The American Gastroenterological association recommends a few non-pharmacological measures and the use of histamine 2 blockers to lessen gastrointestinal symptoms of gastroesophageal reflex disease and the utilization of proton pump inhibitors treatment if there is a definitive indication. Additionally, the American Gastroenterological association's Best Practice Advice statements emphasize deprescribing when there is no clear indication for proton pump inhibitors therapy.

Key Words: *Proton Pump Inhibitors; Cardiovascular Diseases; Risk Factors*

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INTRODUCTION

Proton Pump Inhibitors (PPIs) are antisecretory agents that are used widely to diminish acid secretion. PPIs are prescribed commonly to manage gastric acid-related conditions such as gastroesophageal reflex disease (GERD), gastritis, esophagitis, Barrett esophagus, Zollinger-Ellison syndrome, peptic ulcer disease, nonsteroidal anti-inflammatory drug-associated ulcers, and *Helicobacter pylori* (*H.pylori*) eradication, around the globe.[1] Current PPIs may include omeprazole, esomeprazole, lansoprazole, dexlansoprazole, pantoprazole and rabeprazole.[2] PPIs diminish acid secretion by binding covalently to sulfhydryl groups of cysteines of proton pump in parietal cells of stomach, thereby inactivating H^+/K^+-ATPase (Proton pump).[3]

The most common side effects of PPIs may include headache, constipation, diarrhea, nausea and vomiting.[4] In addition, long-term use of PPIs found to be associated with some serious and rare adverse effects including kidney diseases (acute kidney injury, acute interstitial nephritis, chronic kidney disease, end stage renal disease), car-

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diovascular disease (myocardial infarction, stroke), liver disease (hepatocellular carcinoma), fractures, infections (*Clostridioides difficile* infection, Community-acquired pneumonia, COVID-19), micronutrient deficiencies (hypomagnesemia, anemia, vitamin B12 deficiency, hypocalcemia), dementia, and gastric cancer.[5]

Inappropriate use (overuse or misuse) of PPIs enhances the healthcare cost as well as the risk of polypharmacy and numerous PPI-associated adverse effects. The use of PPIs is increased exponentially in recent decades. Approximately half of the PPI prescriptions found to be with inappropriate indications.[6,7] PPIs are the most widely used drugs around the globe and they are considered one of the top ten most used drugs. Generally, PPIs are misused to prevent gastro-duodenal ulcers in patients without risk factors, overtreatment to manage functional dyspepsia, treatment with antiplatelets or anticoagulants without the risk of gastric injury, stress ulcer prophylaxis in patients not admitted in intensive care units, and steroid alone therapy.[8]

As per previous studies, PPIs are prescribed for up to 70% of cases without any clear indication. According to a prospective observational cross-sectional study conducted in the emergency department, almost one-third of PPI prescriptions were determined to be inappropriate.[9] Similar findings were made by another prospective observational cross-sectional investigation of PPI-using hospitalized patients, which found that almost half of the patients had received their prescriptions for erroneous conditions.[10]

The GI symptoms could be managed non-pharmacologically by various measures including avoidance of meals within 2-3 hours of bedtime, elevation of head of bed, weight loss, cessation of smoking or tobacco products, and avoidance of dietary triggers.[11]

Online databases such as Medline/Pubmed/PMC, Google Scholar, Science Direct, Ebsco, Scopus, Web of science, Embase, and reference lists, were searched using keywords like proton pump inhibitors, renal diseases, acute kidney injury, acute interstitial nephritis, chronic kidney disease, end stage renal disease, cardiovascular disease, myocardial infarction, stroke, liver disease, hepatocellular carcinoma, fractures, infections, *Clostridioides difficile* infection, Community-acquired pneumonia, COVID-19, micronutrient deficiencies, hypomagnesemia, anemia, vitamin B12 deficiency, hypocalcemia, dementia, and gastric cancer to identify relevant publications. The articles published in English are included in this review while discarding the duplicates.

ADVERSE EFFECTS -ASSOCIATED WITH LONG-TERM PPI THERAPY

The long-term use of PPIs is associated with some serious and rare adverse effects including renal diseases (acute interstitial nephritis, acute kidney injury, chronic kidney disease, end stage renal disease), cardiovascular disease (myocardial infarction, stroke), hepatic disease (hepatocellular carcinoma), fractures, infections (*Clostridioides difficile* infection, Community-acquired pneumonia, COVID-19), micronutrient deficiencies (hypomagnesemia, anemia, vitamin B12 deficiency, hypocalcemia), dementia, and gastric cancer (Table 1).

There are no clear definitions of long-term therapy of PPIs. However, prolonged (more than 4-8 weeks) use of PPIs for the management of heartburn, non-erosive esophagitis, mild or moderate GERD could be considered as long-term use of PPIs.[12]

That said, the patients with Barrett's esophagus, severe esophagitis, and history of bleeding gastrointestinal ulcers and the users of long-term non-steroidal anti-inflammatory drugs (NSAIDs) may need long-term therapy of PPIs.[7,11] Consequently, such patients should be monitored for adverse effects associated with the use of long-term PPI therapy.

To avoid inappropriate use of PPIs, the patients who initiated PPI therapy for uninvestigated dyspepsia should be evaluated within 2-4 weeks. The deprescribing of PPI therapy should be considered for the patients who took 4-8 weeks of PPIs and resolved their symptoms and for the patients who have no definitive indication.[7]

The risk of PPI-associated adverse effects is higher among the patients with advanced age, comorbid conditions, concomitant medications, and others. The elderly population is already at risk of developing many complications that could be aggravated by PPI therapy. Regular monitoring is indicated in elderly PPI users to determine the need of PPI therapy continuation.[13]

Few concomitant medications such as metformin, diuretics, etc. may enhance PPI-associated adverse effects. Concurrent use of PPI and metformin may lead to diminished absorption of vitamin B12 resulting in vitamin B12 deficiency.[14] Similarly, the risk of hypomagnesemia found to be higher among the patients using a PPI and a diuretic concomitantly.

1. Renal problems

A number of studies have found a connection between PPIs and the onset of renal diseases like acute interstitial nephritis (AIN), acute kidney injury (AKI), chronic kidney disease (CKD), and end-stage renal disease (ESRD).[7]

Some studies have hypothesized that the accumulation of PPIs or their metabolites in the tubule-interstitium could trigger a cell-mediated immune response, resulting in an inflammatory infiltrate and AIN, which could cause AKI, interstitial fibrosis, or tubular atrophy, all of which could result in CKD and ESRD. Moreover, long-term use of PPIs is associated with hypomagnesemia that could result in endothelial cell dysfunction, accelerated endothelial senescence, enhanced oxidative stress, hyperinflammation, and vascular senescence and subsequent progression of kidney disease.[15]

1) Acute interstitial nephritis (AIN): An inflammatory infiltration in the renal interstitium is the defining feature of AIN, and patients may have symptoms such as oliguria, lethargy, anorexia, weight loss, nausea, and vomiting.

TABLE 1. PPI therapy-associated adverse effects

S.No	Serious side effects	Probable mechanism(s) of pathogenesis
1	Renal problems (AIN, AKI, CKD, ESRD)	Deposit of PPIs or their metabolites in tubulo-interstitium may induce cell-mediated immune response causing interstitial inflammatory infiltrate and AIN that may result in CKD and ESRD via AKI and interstitial fibrosis and tubular atrophy[15]
2	Cardiovascular risks (MACE, MI, stroke)	Elevated plasma asymmetric dimethylarginine (ADMA) levels causing inhibition of vascular nitric oxide generation by inhibiting nitric oxide synthase enzyme, decreased vitamin C and vitamin B12 levels, hypomagnesemia and hypocalcemia-related arrythmia, and endothelial dysfunction[42]
3	Fractures	More insoluble state of calcium and diminished absorption of calcium due to suppressed acid secretion-associated hypochlorhydria and hypergastrinemia[63]
4	Infections (*C.difficile* infection, CAP, COVID-19)	Hypochlorhydria-associated diminished protective effect, suppressed immune system, and small intestinal bacterial overgrowth due to suppressed gastric acid secretion[75]
5	Micronutrient deficiencies (hypomagnesemia, anemia, vitamin B12 deficiency, hypocalcemia, hypokalemia)	Impaired intestinal absorption of magnesium via decreased solubility of magnesium in intestinal lumen, altered expression and activity of key transporter proteins, and dysbiosis of gut microbiome[84]
6	Hypergastrinemia	Hypochlorhydria or achlorhydria induced by PPIs-associated gastric acid suppression, stimulates G cells in the gastric antrum to release gastrin resulting in hypergastrinemia[94]
7	Cancer (gastric cancer, pancreatic cancer, colorectal cancer, hepatic cancer)	Potent acid suppression by PPIs may ensue in gastric cancer via worsening gastric atrophy, hypergastrinemia, ECL hyperplasia, and bacterial overgrowth[99]
8	Hepatic encephalopathy	Unknown
9	Dementia	Unknown

According to a nested case-control study from New Zealand, current PPI users had a significantly higher chance of developing AIN.[16] Similar to this, a number of retrospective analyses showed a link between the onset of AIN and PPIs like lansoprazole and omeprazole.[17-20] Moreover, a number of cases of PPI-related AIN have been documented.

2) Acute kidney injury (AKI): Acute renal failure (ARF), often known as AKI, is the sudden or rapid loss of a kidney's filtration ability. Reduced urine production, fluid retention, breathlessness, weakness, an irregular pulse, confusion, and nausea are some of the signs and symptoms of AKI. PPI users had a greater risk of AKI, according to many nested case-control studies.[21,22] Moreover, a population-based investigation showed that starting PPI in individuals 66 years of age or older increased the incidence of AKI.[23] Similar to this, many cohort studies have demonstrated the elevated risk of AKI in PPI-using individuals.[24,25] In addition, a meta-analysis of cohort studies and case-control studies emphasizes that PPI users have shown a greater prevalence of AKI.[26]

The number of deaths, life-threatening events, hospitalizations, and disability events related to PPI use were higher due to PPI-associated AKI than PPI-associated CKD, according to analyses of adverse reports of AKI and CKD associated with the use of PPIs in the United States (US) Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database from 2004 to 2019.[27-29]

3) Chronic kidney disease (CKD): CKD is a progressive loss of renal function over time that is characterized by increased or decreased urination, fatigue, dry skin, appetite loss, anemia, muscular cramps, nausea, headaches, shortness of breath, weight loss and other symptoms.[30] According to two distinct retrospective case-control designs, PPI users had an increased risk of incident CKD and death.[31] Also, a long-running population-based cohort study (Atherosclerosis Risk in Communities (ARIC) study) discovered that PPI users had a greater risk of developing incident CKD.[32] The use of PPIs was also linked to an increased risk of incident CKD and a drop in estimated glomerular filtration rate (eGFR), according to an analysis of national datasets from the Department of Veterans Affairs.[33]

Furthermore, a retrospective analysis of the Stockholm creatinine measurements database showed that the start of PPI therapy and cumulative PPI exposure increased the risk of CKD progression.[34] PPIs are also linked to an increased risk of CKD in diabetic patients, according to a population-based retrospective cohort study of diabetic database data from the National Health Insurance Research Database.[35] Moreover, a retrospective cohort study found that PPI use increased the risk of incident CKD.[36] Also, two population-based retrospective cohort studies found that PPI users had a greater risk of incident CKD.[37,38]

4) End stage renal disease (ESRD): The fifth and final stage of CKD, known as ESRD, occurs when the eGFR drops below 15 ml/min. ESRD symptoms include exhaustion, itchy skin, constipation, anorexia, discomfort, disturbed sleep, anxiety, dyspnea, nausea, depression, and others.[39] Among individuals with renal disorders, PPI consumption increased the incidence of ESRD, as was seen in

a case-control research using the Taiwan National Health Insurance Research Database.[40] Also, it was discovered through a study of national databases maintained by the Department of Veterans Affairs that PPI use increased the risk of incident CKD, CKD progression, and ESRD.[41]

2. Cardiovascular risks

Several studies have demonstrated a link between PPI exposure and the prevalence of cardiovascular disorders such as major adverse cardiovascular events (MACE), myocardial infarction, stent thrombosis, and stroke. PPI-associated enhanced risk of adverse cardiovascular outcomes may occur via various mechanisms including elevated plasma asymmetric dimethylarginine (ADMA) levels causing inhibition of vascular nitric oxide generation by inhibiting nitric oxide synthase enzyme, decreased vitamin C and vitamin B12 levels, hypomagnesemia and hypocalcemia-related arrythmia, and endothelial dysfunction.[42]

1) Major adverse cardiovascular events (MACE): Patients who took PPIs for GERD had a 70% higher risk of serious cardiovascular events, according to a meta-analysis of seventeen randomized controlled clinical trials.[43] The risk of major adverse cardiovascular events (MACE), myocardial infarction, stent thrombosis, and target vessel revascularization was also raised in PPI users, according to a meta-analysis of eleven studies.[44] A meta-analysis of seven observational studies also revealed a link between PPI use and an increased risk of adverse cardiovascular events.[45] Another meta-analysis of fifteen randomized controlled clinical trials found that PPI users had a significantly greater risk of MACE, myocardial infarction recurrence, stent thrombosis, target vessel revascularization, and stroke.[46] Also, results from a meta-analysis of 33 observational studies revealed that the risk of adverse clinical outcomes was increased in users of PPIs.[47]

On the other hand, a meta-analysis of sixty-six studies failed to identify a link between the use of PPIs and the emergence of MACE.[48] Another meta-analysis of 19 randomized controlled clinical trials found no evidence of a significant increase in the incidence of major adverse cardiovascular and cerebrovascular events (MACCE), all-cause death, cardiovascular death, myocardial infarction, stent thrombosis, or gastroduodenal ulcer.[49] Nevertheless, no discernible rise in cardiovascular adverse events linked to PPI usage was found in a meta-analysis of eleven observational studies.[50]

2) Myocardial infarction (MI): Increased levels of asymmetrical dimethylarginine (ADMA) caused by the use of PPIs is hypothesized to increase the risk of myocardial infarction by blocking the enzyme dimethylarginine dimerhylaminohydrolase (DDAH). Nitric oxide synthase is blocked by ADMA, which leads to a decrease in NO production, increased vascular contraction, and decreased vascular relaxation.[51]

An increased risk of myocardial infarction was seen in new PPI users, according to a nested case-control study from the United Kingdom (UK).[52] Long-term or high-dose PPI use increased the risk of new-onset acute myocardial infarction in patients who did not have a history of ischemic heart disease, according to another nested case-control research involving 27,624 patients.[53]

Additionally, a meta-analysis of six randomized controlled clinical trials, two post-hoc analysis, and two observational studies showed a positive correlation between the use of PPIs and the incidence of myocardial infarction and other cardiovascular issues.[54]

A self-controlled case series from Hong Kong, on the other hand, found no correlation between PPI use and the occurrence of myocardial infarction.[55] Moreover, a German cohort of new PPI users did not uncover any proof that PPI usage increased the risk of myocardial infarction.[56]

3) Stroke: The use of PPIs raises the risk of stroke by raising plasma levels of ADMA and lowering NO levels.[57] Furthermore, a multivariate Cox regression analysis showed that long-term PPI usage is linked to the development of cerebral small vascular disease (SVD) and deep white matter hyperintensities (WMH), which can lead to stroke or cognitive decline.[58]

The risk of first-time ischemic stroke and myocardial infarction increased in long-term users of PPI, according to a retrospective Danish nationwide cohort study of 214, 998 individuals.[59] The use of PPIs was found to be positively associated with an increased risk of hospitalization for ischemic stroke in another retrospective nationwide cohort study from Taiwan.[60] Also, a prospective analysis of participants from the UK Biobank (492,479) revealed that the regular use of PPIs was associated with a 16% increased risk of stroke compared to non-users of PPIs.[61]

PPI use increases the incidence of stroke, according to a meta-analysis of 13 observational cohort studies and a case-control study.[62] Also, a meta-analysis of nine high-quality randomized controlled clinical trials revealed a positive correlation between the usage of PPIs and the incidence of stroke.[61]

3. Fractures

The long-term use of PPIs is also linked to an increased risk of hip, spine, and wrist fractures, according to numerous earlier studies. The increased risk of fractures may be caused by more insoluble calcium and decreased calcium absorption as a result of hypochlorhydria and hypergastrinemia caused by inhibited acid secretion.[63]

The use of PPIs was found to slightly increase the incidence of hip, spine, and any-site fractures in a meta-analysis of eleven case-control/cohort studies.[64] In a similar vein, a second meta-analysis of 18 studies, including 9 case-control studies and 9 prospective observational studies, found that PPI use increased the risk of fractures (hip, spine, and any-site fractures). PPI use has been linked to an increased incidence of hip fracture in fifteen of these studies.[65] Moreover, in May 2010, the U.S. Food and Drug Administration (FDA) has issued a safety alert regarding an association between the use of PPI and elevated risk of fractures of hip, wrist and spine.[66]

4. Infections

Long-term PPI use has been linked to an increase in the incidence of infections such as *Clostridium difficile* infection, community-acquired pneumonia (CAP), and Coronavirus disease 2019 (COVID-19). PPI use affects the gut microbiota, which is necessary for reducing bacterial growth or boosting the immune system.

1) *Clostridioides difficile* infection: PPIs have been linked to an increased risk of *Clostridioides difficile* infection, according to a number of studies. As PPIs raise gastric pH, PPI-associated alkaline intestine pH may facilitate *C. difficile* sporulation.[67]

Long-term use of PPIs is positively associated with *C. difficile* infection, according to numerous systematic reviews and meta-analyses that examined a large number of observational studies, including case-control and cohort studies on thousands of patients.[68] Additionally, a meta-analysis of ten case-control studies and six cohort studies revealed that PPI users had significantly higher rates of *C. difficile* recurrence.[69] In addition, the FDA released a safety advisory regarding PPI-associated *C. difficile* infection in February 2012.[70]

2) Community-acquired pneumonia (CAP): Positive association of the use of PPI and a heightened risk of community-acquired pneumonia (CAP) has been established in several studies. PPI users may be at greater risk for developing CAP due to aspiration of acid-labile pathogenic bacteria and increased bacterial colonization of larynx, esophagus and lungs.[71]

PPI medication significantly increases the incidence of pneumonia, according to a meta-analysis of 10 randomized controlled clinical trials and 48 observational studies.[72] Another meta-analysis of seven observational studies found a strong correlation between PPI use and the probability of developing CAP.[73] Moreover, a meta-analysis of 13 studies, including 7 case-control studies, 4 cohort studies, and 2 observational studies, found that patients taking PPI had a higher chance of developing CAP than those who did not.[74]

3) Coronavirus disease 2019 (COVID-19): The use of PPIs raised the risk of the coronavirus disease 2019 (COVID-19) infection and its mortality, according to numerous research studies. Various reasons have been proposed for the association of PPIs and COVID-19 severity that include hypochlorhydria-associated diminished protective effect, enhanced survival of severe acute respiratory syndrome coronavirus-2 (SARS CoV-2) virus in stomach, suppressed immune system, and small intestinal bacterial overgrowth due to suppressed gastric acid secretion.[75]

According to a meta-analysis of six observational studies, current PPI users have a significantly higher risk of developing COVID-19 as well as dying from it.[76] Similarly, in another meta-analysis, which included twelve observational retrospective cohort studies, the poor outcome in PPI-using patients was quantified.[77] Also, a meta-analysis of four case-control studies and 10 cohort studies found a significantly enhanced risk of severity and mortality of COVID-19 infection in current users of PPIs.[75] Furthermore, a meta-analysis of fifteen observational retrospective cohort studies determined a significantly higher risk of severe outcomes in patients with COVID-19 due to the current use of PPIs.[78]

5. Micronutrient deficiencies

The long-term use of PPIs has been linked to micronutrient deficiencies like hypomagnesemia, anemia, vitamin B12 deficiency, and hypocalcemia, according to previous studies.

1) Hypomagnesemia: There have been a number of reports regarding hypomagnesemia brought on by PPIs. Also, the U.S. Food and Drug Administration (FDA) released a safety advisory in March 2011 addressing hypomagnesemia linked to PPIs.[79]

A meta-analysis of nine retrospective observational studies found that using PPIs may increase the incidence of hypomagnesemia.[80] Also, a meta-analysis of five cross-sectional studies, three cohort studies, and a case-control study revealed a link between using PPIs and an increased risk of hypomagnesemia.[81] Furthermore, a meta-analysis of 16 observational studies, including 13 cross-sectional studies, 2 case-control studies, and 1 cohort study, discovered that patients taking PPIs significantly increased their risk of hypomagnesemia.[82] On the other hand, a meta-analysis of fifteen research found a hazy relationship between PPI and the incidence of hypomagnesemia.[83]

PPI-associated hypomagnesemia has been linked to a number of different mechanisms, including impaired intestinal absorption of magnesium via decreased solubility of magnesium in intestinal lumen, altered expression and activity of key transporter proteins, and dysbiosis of gut microbiome.[84]

2) Anemia: PPI-associated anemia has been documented in numerous case reports and observational studies. Many different mechanisms, including iron malabsorption that may result from PPI-induced hypochlorhydria, have been hypothesized for the development of PPI-associated anemia.[85] PPIs may restrict the absorption of iron by upregulating the peptide hormone hepcidin, which is known to regulate iron metabolism and block the cellular iron exporter duodenal ferroportin.[86]

Iron deficiency was found to have favorable dose-response and time-response correlations in patients taking PPIs, according to a population-based case-control research.[87] Moreover, a meta-analysis of fourteen studies found that long-term PPI users have an elevated risk of iron deficiency anemia.[88]

3) Vitamin B12 deficiency: A positive association between Vitamin B12 deficiency and PPI use has been found in numerous cross sectional and cohort studies. For vitamin B12 insufficiency linked to PPIs, various mechanisms have been put forth. PPIs lessen the production of stomach acid, which is necessary for pepsinogen to turn into pepsin, which releases vitamin B12 from dietary proteins. Pepsi-

nogen is converted into pepsin by the action of pepsinogen. Vitamin B12 absorption is ultimately decreased as pepsin production declines.[89]

Long-term PPI use has been linked to the emergence of vitamin B12 insufficiency, according to a single-center cohort study.[90] Moreover, an observational study showed that PPI users had a greater prevalence of vitamin B12 deficiency.[91] The use of PPIs is also linked to a rise of vitamin B12 deficiency, according to a meta-analysis of four case-control studies and one prospective cohort study.[92]

4) Hypocalcemia and hypokalemia: Hypocalcemia and hypokalemia are significantly associated with PPI users, according to an analysis of more than ten million reports from the FDA Adverse Event Reporting System (FAERS). PPI use over an extended period of time may reduce calcium absorption, resulting in hypocalcemia. Moreover, hypokalemia in PPI users may be facilitated by PPI-associated CKD.[93]

6. Hypergastrinemia

Hypochlorhydria or achlorhydria induced by PPIs-associated gastric acid suppression, stimulates G cells in the gastric antrum to release gastrin resulting in hypergastrinemia.[94] Hypergastrinemia may induce rebound hypersecretion of acid once PPIs are discontinued. Hypergastrinemia-associated rebound hyperacidity may cause dyspeptic symptoms and reintroduction of PPIs.[95] Patients taking PPIs for a prolonged period of time had moderate hypergastrinemia, according to a systematic review of 16 studies.[96] Hypergastrinemia may also induce hyperplasia of enterochromaffin-like (ECL) cells in oxyntic mucosa, gastric cancer and other PPI-related adverse effects.[97]

7. Cancers

Long-term use of PPIs may enhance the incidence of cancers including gastric cancer, pancreatic cancer, colorectal cancer and hepatic cancer. An umbrella review of twenty-one meta-analyses that analyzed 65 observational studies concluded that PPI users had a significantly higher risk of developing malignancies like gastric, pancreatic, colorectal, and hepatic cancer.[98]

1) Gastric cancer: The extended use of PPIs is positively associated with the emergence of gastric cancer, according to several observational studies. Those taking PPIs for a prolonged period of time showed a more than two-fold increased risk of gastric cancer incidence. There have been several hypothesized mechanisms for PPI-associated gastric cancer. Potent acid suppression by PPIs may ensue in gastric cancer via increasing gastric atrophy, hypergastrinemia, ECL hyperplasia, and bacterial overgrowth.[99]

A positive association between long-term PPI use and increased risk of fundic gland polyps and gastric cancer was found by performing a meta-analysis of twelve studies, which included a randomized controlled trial, four case-control studies, and seven cohort studies.[100] Corresponding to this, a meta-analysis of 926,386 patients found that long-term PPI users had a twofold greater chance of developing gastric cancer.[101] Also, a meta-analysis of seven trials with a combined total of 943,070 individuals found that long-term PPI use was linked to an increased risk of gastric cancer.[102] Moreover, a meta-analysis of two randomized clinical trials and twelve non-randomized studies involving more than 6 million patients revealed that the evidence of enhanced risk of gastric cancer associated with the long-term use of PPIs was minimal.[103]

The risk of gastric cancer was doubled in PPI users according to a meta-analysis of eight case-control studies and five retrospective cohort studies.[104] In addition, a meta-analysis of eighteen studies involving 4,348,905 patients found that PPI users had an increased risk of stomach cancer.[105] Moreover, a meta-analysis of thirteen observational studies determined a link between PPI use and the occurrence of gastric cancer.[106] Furthermore, a meta-analysis of sixteen cohorts and case-control studies found that the risk of gastric cancer was significantly elevated in patients taking PPIs.[107]

2) Pancreatic cancer: Various observational studies including a nationwide case-control study based on the French National Health Data System (SNDS),[108] a population-based nationwide Swedish cohort study,[109] a nested case-control study and a retrospective cohort study in The Health Improvement Network (THIN),[110] and a twelve-year longitudinal population-based study using the Korean National Health Insurance Corporation claims database[111] found a link between PPI use and the incidence of pancreatic cancer. PPI-associated hypergastrinemia, hypochlorhydria-associated bacterial overgrowth, and other mechanisms may all increase the risk of pancreatic cancer.[111]

The risk of pancreatic cancer increased due to the use of PPIs, revealed by a meta-analysis of eight case-control and three cohort studies.[112] Similarly, a meta-analysis of seven case-control studies and three cohort studies demonstrated that the risk of pancreatic cancer was significantly enhanced in PPI users.[113] In addition, a meta-analysis of one randomized controlled clinical trial, two cohort studies and five nested case-control studies demonstrated that the use of PPIs was positively associated with enhanced risk of pancreatic cancer.[114] Moreover, a nested case-control study determined that the risk of pancreatic cancer was elevated in PPI users.[115] In contrast, no conclusive evidence of PPI-associated pancreatic cancer was observed in a meta-analysis of six case-control and cohort studies.[116]

3) Colorectal cancer: The long-term use of PPIs has increased the risk of colorectal cancer. Long-term PPI use was found to be linked to higher all-cause and colorectal cancer-specific mortality in a population-based cohort analysis conducted in Sweden.[117] By causing hypergastrinemia, which can cause colonic and rectal cells to proliferate, prolonged PPI usage may increase the risk of colorectal cancer.[118] Moreover, PPI-associated hypergastrinemia, activation of the Yes-associated protein (YAP), altered gut flora, and fecal alkalization may all contribute to the growth and spread of colorectal cancer.[119]

A substantial correlation between the risk of colorectal cancer and PPI usage was not found, according to the findings of three sizable prospective cohort studies.[120] Also, a meta-analysis of three cohort studies and six case-control studies found a slight correlation between the risk of colorectal cancer and prolonged use of PPIs.[121]

4) Hepatic cancer: Hepatocellular carcinoma risk may rise with prolonged PPI use. A favorable correlation between the use of PPIs and a greater risk of hepatocellular carcinoma was found in a nested case-control study from Taiwan. PPI-associated hypergastrinemia may increase the risk of hepatocellular cancer.[122] Among patients with chronic liver disease who took PPIs, there was an increased risk of hepatocellular carcinoma and mortality, according to a meta-analysis of eleven trials.[123]

On the other hand, a Korean observational study that examined data from the National Health Insurance Service revealed no increased risk of hepatocellular carcinoma among PPI users.[124] Moreover, a meta-analysis of five studies found no evidence that taking PPIs increased the chance of developing hepatocellular carcinoma.[125]

8. Hepatic encephalopathy

Patients with chronic liver disease have seen a number of negative clinical consequences as a result of PPI use. The use of PPIs was linked to a number of unfavorable clinical outcomes in patients with chronic liver disease, according to a meta-analysis of 47 observational studies, including 35 cohort studies and 12 case-control studies.[126] Furthermore, a meta-analysis of three case-control studies found a link between PPI usage and an increased risk of hepatic encephalopathy in individuals with acute liver dysfunction.[127] A meta-analysis of nine observational studies, including five case-control studies and four cohort studies, found that the risk of hepatic encephalopathy was significantly elevated in patients with advanced liver disease who used PPIs.[128] Likewise, a meta-analysis of four case-control studies and three cohort studies demonstrated that the use of PPIs in patients with liver cirrhosis increases the risk of hepatic encephalopathy.[129] Furthermore, a meta-analysis of ten observational studies found a positive association between the use of PPIs and elevated risk of hepatic encephalopathy in patients with hepatic cirrhosis.[130]

9. Dementia

The likelihood of dementia in PPI users has been assessed by numerous observational studies. PPI users have a considerably higher risk of dementia, according to a meta-analysis of six cohort studies.[131]

In contrast, no statistically significant link between increased risk of dementia and PPI use was found in meta-analyses of six cohort studies,[132] ten independent studies,[133] four case-control studies and eight cohort studies,[134] seventeen observational studies,[135] eleven observational studies,[136] one randomized controlled clinical trial, and five prospective observational studies[137] and nine observational studies.[138]

The level of evidence of adverse effects-associated with long-term PPI therapy is low as most of the studies discussed here are observational in nature and most findings need to be confirmed by randomized controlled clinical trials. Inappropriate use of PPI, such as overuse, misuse, high-dose PPIs without definitive indication, and off-label prescriptions, should be curbed. To manage mild-moderate symptoms, PPIs should always be used for the shortest possible duration at the smallest effective dose. However, the patients with definitive indications should continue long-term use of PPIs with regular monitoring.

AMERICAN GASTROENTEROLOGICAL ASSOCIATION (AGA) RECOMMENDATIONS

The recommended duration of PPI therapy for the management of patients with GERD, *H.pylori* infection, and peptic ulcer disease is limited to 2-12 weeks, while indefinite PPI therapy may be indicated in the management of patients with Barrett's esophagus and severe esophagitis.[139] The American Gastroenterological association (AGA) offers various evidence-based recommendations (Table 2) to manage patients with GERD that include replacing PPIs with histamine 2 blockers, administration of PPIs 30-60 minutes before meal rather than at bedtime, indefinite PPI maintenance therapy to manage Los Angeles grade C or D esophagitis, no baclofen therapy without any objective evidence of GERD, avoidance of prokinetic agent use without any objective evidence of gastroparesis, no sucralfate therapy for GERD except during pregnancy, weight loss in overweight and obese patients, avoiding meals within 2-3 of bedtime, elevating the head of the bed, quitting smoking and tobacco products, avoidance of "trigger foods", deprescribing of PPI if possible, use of lowest possible PPI maintenance dose, and avoidance of routine addition of medical therapies in PPI non-responders.[140]

Moreover, Best Practice Advice (BPA) statements from the AGA on deprescribing PPIs therapy (Table 3) recommend that the primary care provider should review indications of PPI use on a regular basis, deprescribing of PPI therapy should be considered if there is no definitive indication, patients taking-twice daily doses of PPI for long-term should be considered for a once-daily dose, deprescribing of PPI therapy should not be considered for patients with certain conditions including severe erosive esophagitis, esophageal ulcer, peptic stricture, Barrett's esophagus, eosinophilic esophagitis, or idiopathic pulmonary fibrosis, the risk of upper gastrointestinal (GI) bleeding should be assessed before PPI deprescribing consideration, deprescribing of PPI therapy should not be considered for patients with heightened risk of upper GI bleeding, PPI deprescribing-associated rebound acid hypersecretion may induce transient upper GI symptoms and patients should be advised on this regard, dose tapering or abrupt discontinuation of PPI should be considered in deprescribing process, and deprescribing of PPI should not be done

TABLE 2. AGA recommendations on PPI therapy in the management of GERD[140]

S.No	Recommendations from AGA
1	Substitution of PPIs with histamine 2 blockers
2	Administration of PPIs 30-60 minutes before meal rather than at bedtime
3	Indefinite PPI maintenance therapy to manage Los Angeles grade C or D esophagitis
4	No baclofen therapy without the objective evidence of GERD
5	No prokinetic agent use without the objective evidence of gastroparesis
6	No sucralfate therapy for GERD except during pregnancy
7	Weight loss in overweight and obese patients
8	Avoidance of meals within 2-3 of bedtime
9	Elevation of head of bed
10	Cessation of smoking and tobacco products
11	Avoidance of "trigger foods"
12	Deprescribing of PPI if there is no definitive indication
13	Use of lowest possible PPI maintenance dose
14	Avoidance of routine addition of medical therapies in PPI non-responders

TABLE 3. Best Practice Advice (BPA) statements from the AGA on deprescribing PPI therapy[141]

S.No	BPA statements from AGA
1	The primary care provider should review indications of PPI use regularly
2	Deprescribing of PPI therapy should be considered if there is no definitive indication
3	Deprescribing of PPI therapy should not be considered for patients with certain conditions including severe erosive esophagitis, esophageal ulcer, peptic stricture, Barrett's esophagus, eosinophilic esophagitis, or idiopathic pulmonary fibrosis
4	The risk of upper gastrointestinal (GI) bleeding should be assessed before considering PPI deprescribing
5	Deprescribing of PPI therapy should not be considered for patients with heightened risk of upper GI bleeding
6	PPI deprescribing-associated rebound acid hypersecretion may induce transient upper GI symptoms and patients should be advised on this regard
7	Dose tapering or abrupt discontinuation of PPI should be considered in deprescribing process
8	Deprescribing of PPI should not be done based on PPI-associated adverse events

based on PPI-associated adverse events.[141]

DISCUSSION

Clinicians, including prescribers and pharmacists, should be aware of the adverse effects associated with long-term use of PPIs such as renal disorders (AIN, AKI, CKD, ESRD), cardiovascular risks (MACE, MI, Stroke), fractures, infections (*c,difficile* infection, CAP, COVID-19), micronutrient deficiencies (hypomagnesemia, anemia, vitamin B12 deficiency, hypocalcemia, hypokalemia), hypergastrinemia, cancers (gastric cancer, pancreatic cancer, colorectal cancer, hepatic cancer), hepatic encephalopathy, and dementia. In addition, the patients taking PPIs for long-term should be monitored for the listed adverse effects. The AGA recommends some non-pharmacological measures and use of histamine 2 blockers to reduce GI symptoms of GERD and the use of PPI therapy if there is definitive indication. Moreover, BPA statements from the AGA emphasize on deprescribing if there is no definitive indication for PPI therapy.

CONFLICT OF INTEREST STATEMENT

None declared.

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