Morris and Nighot
Bulletin of the National Research Centre (2023) 47:134
https://doi.org/10.1186/s42269-023-01107-9

Bulletin of the National Research Centre

REVIEW

Open Access

Understanding the health risks and emerging concerns associated with the use of long-term proton pump inhibitors

Nathan Morris[1*] and Meghali Nighot[1]

Abstract

Background Proton pump inhibitors (PPIs) are the most efficacious and common medications for gastric acid suppression. However, PPIs continue to perpetuate safety concerns due to the availability as an over-the-counter medication. This uncontrolled use of PPIs has recently been shown to be associated with the increased health risks.

Main body of the abstract The inhibition of gastric acid production by irreversibly binding to and inhibiting the H^+/K^+ ATPase enzyme system can cause structural and physiologic changes in the GI microbiome, GI physiology, and pH. With the recent guideline updates from American Gastroenterological Association regarding deprescription of PPIs, this review focuses on the complications of long-term use of PPIs on various systems, gut microbiome, intestinal barrier and inflammatory bowel disease (IBD).

Short conclusion If PPI use in IBD patients is associated with increased risk of other adverse outcomes, considering the PPI-associated mineral, electrolyte and microbial alterations also needs rigorous evaluation.

Keywords Inflammatory bowel disease, Microbiome, Gastrointestinal pH, Nutrient absorption, Hydrogen/potassium ATPase, Intestinal barrier, Dementia, Cardiovascular disease

Background

Proton pump inhibitors (PPIs) block the H^+/K^+ATPase enzyme system in the gastric parietal cells. As a treatment for gastroesophageal reflux disease (GERD) and associated conditions, proton pump inhibitors are the second most prescribed drug class in the USA (Mullin et al. 2009). PPI-induced elevation in intra-gastric pH and subsequent alterations of gastrointestinal physiology are known to cause undesired effects on the entire GI tract. Nevertheless, PPIs are generally well tolerated and safe medications. They are commonly prescribed medications for a variety of gastrointestinal ailments including gastroduodenal ulcer, erosive esophagitis, gastroesophageal reflux disease, gastric hypersecretory syndromes and included in the treatment of *Helicobacter pylori*. PPIs are often recommended to patients in the hospital setting as prophylaxis against gastrointestinal ulcers that can be brought on by stress and/or additional medications (Lo and Chan 2013). Millions all over the world use PPIs every year whether prescribed or over the counter with the most popular PPI being omeprazole. Omeprazole was responsible for about 57% of the total prescriptions of PPIs in 2019 (https://clincalc.com/DrugStats/Drugs/Omeprazole). The average number of prescriptions per year is around 113 million worldwide costing around 13 billion dollars (Sarnaik et al. 2021). PPIs work by inhibiting the hydrogen/potassium pump (H^+/K^+ ATPase pump) which inhibits the secretion of hydrogen by parietal cells and subsequently the uptake of extracellular potassium. Therefore, this mechanism inhibits acid secretion from gastric parietal cells. Because of the

*Correspondence:
Nathan Morris
nmorris2@pennstatehealth.psu.edu
[1] Department of Gastroenterology, Penn State College of Medicine, Hershey, USA

inhibition of acid secretion, PPIs are prescribed to treat and prevent acid reflux, gastroesophageal reflux disease (GERD), ulcers, and to lessen harmful impacts on the stomach and/or intestines caused by other prescription drugs. However, because of their generally safe nature, PPIs can often be overprescribed and used long-term. The definition for long-term use of PPIs can vary as evidenced in this review which can lead to more difficult interpretation of study results. The American Gastroenterological Association (AGA) recently published Best Practice Advice (BPAs) on the clinical use of PPI therapy in hopes to lessen the inappropriate prescriptions of PPIs (Targownik et al. 2022). These medications are often used to treat conditions where PPI use has not yet been proven beneficial and are often used for long term treatment. According to Hayes et al., it is estimated that around 65% of patients using PPI treatment have no indication of need (Hayes et al. 2019). To better understand the threat that overuse of PPIs pose to the population, it is beneficial to look at the possible outcomes through previous issues that have occurred. For example, the over prescription of antibiotics became a threat as antibiotics were found to disrupt the gut microbiome decreasing the diversity and richness of the gastrointestinal microbiota (Sun et al. 2019). Recent studies have shown that the overuse of PPIs is linked to a variety of health conditions, not only limited to the disruption of the gut microbiome, which induces new and significant safety concerns regarding these drugs.

Another important factor is the over-usage of PPIs in the elderly population. In a study investigating the use of PPIs among nursing home patients in the USA, it was found that 27% of nursing home patients were using PPIs (Rane et al. 2017). Of this same population, it was found that about 49% of these prescriptions were not evidence based. While some studies have not shown conclusive data or have shown contradictions, there are a number of health conditions that are proven to be associated with the long-term and overuse of PPIs. Further research is warranted in order to evaluate the use of PPIs and the potential side effects more accurately. Nevertheless, the most commonly found side effects of long-term and/or overuse of PPIs are described further. Figure 1 and Table 1 depict the effected systems and side effects, respectively, associated with long-term PPI use.

Main text

Mechanism of action of PPIs

The stomach maintains a low pH to digest food and to aid in protection against pathogens. Such pH values are maintained by the secretion of hydrogen chloride (HCl) by the parietal cells. The cellular aerobic metabolism results in the production of carbonic acid which can then supply H^+ ions by dissociation. These ions are then transported into the lumen of the stomach by the H^+/K^+ ATPase pump in exchange for potassium. Bicarbonate is exchanged for chloride from the blood on the basolateral side of the parietal cell and the Cl- ions are transported to the lumen of the stomach to form HCl. Figure 2 depicts an overview of the mechanism of action of proton pump inhibitors described here.

There are intrinsic ways to both increase and decrease acid production in the stomach in response to various stages of digestion process and other stimulations and responses. When these intrinsic methods are not successful, medications such as PPIs can be administered to control excessive acid production. Because PPIs are weak bases, they accumulate in the acidic spaces of the stomach where parietal cells are active. This acidity is important as PPIs are prodrugs and require acid to become activated. Different PPIs bind to varying cysteine residues of the H^+/K^+ ATPase allowing for slightly different properties of the PPIs (Shin and Sachs 2008). Because PPIs inhibit the gastric H^+/K^+ ATPase by irreversible covalent bonding, they are able to produce a long-lasting effect. However, due to gastric H^+/K^+ ATPase turnover, not all H^+/K^+ ATPase pumps can be blocked, and it may take several days of administration of PPIs to reach an optimal effect. It is estimated that once-a-day administration of PPIs results in about a 66% maximum inhibition of acid suppression (Shin and Sachs 2008). Because PPIs inhibit gastric H^+/K^+ ATPase, which is the final step in acid secretion, it is recognized as the best medicine available to inhibit acid secretion. However, due to increasing studies correlating PPI usage with side effects that range in severity, there may need to be greater regulation in how PPIs can be prescribed.

Long-term PPI use risks

Clinically, the conditions caused by the long-term and overuse of PPIs can impact various body systems. The systems affected can include the gastrointestinal tract, the respiratory system, the skeletal-muscular system, the immune system, the urinary system, and the nervous system. These systems are affected by different mechanisms caused by PPIs such as nutrient deficiencies, changes in pH, and overgrowth of gastrointestinal microbes to name a few. Studies have also shown that long-term and overuse of PPIs can cause damage to the gut mucosa as well. These changes may lead to an increased risk of gastrointestinal cancers (Kinoshita et al. 2018). The risks of long-term and/or overuse of PPIs are further discussed in relation to the body system affected.

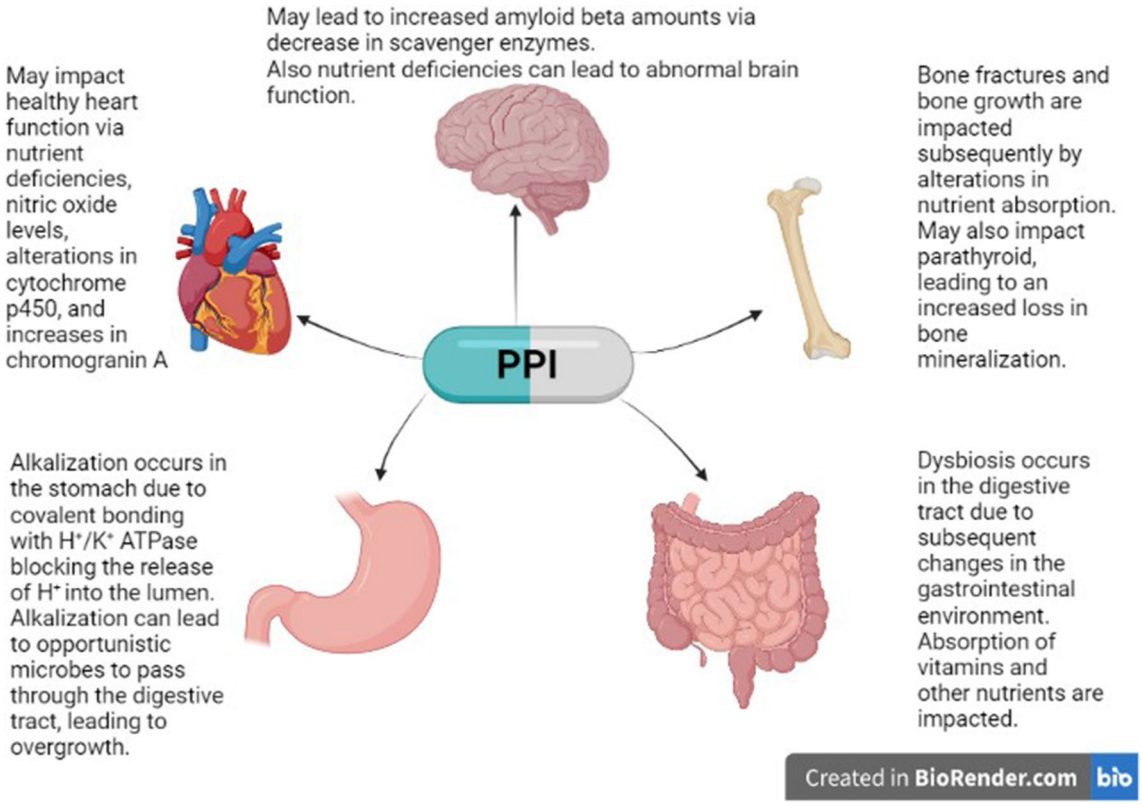

Fig. 1 Proposed mechanisms of long-term PPI use effects on the body. PPIs work by inhibiting the acidification of the stomach via covalent bonding to the H^+/K^+ ATPase, allowing for the passage of opportunistic microbes through the stomach. Subsequent alterations via PPI use in the gastrointestinal environment cause dysbiosis as well as direct and indirect hindrance in the absorption of vitamins and nutrients. PPI use can also impact bone growth and density as nutrient absorption is hindered. Use of PPIs may impact the parathyroid hormone, leading to an increase loss in bone mineralization. Increases in amyloid beta amounts and nutrient absorption leading to abnormal brain function. Cardiac function is also impacted by PPI use, as nitric oxide levels, nutrient deficiencies, cytochrome p450, and chromogranin A can be impacted

Long-term PPI use effect on the nervous system

Dementia is a neurological condition that involves the progressive loss of cognitive abilities and can negatively impact the individual as well as the individual's support system. Alzheimer disease (AD), a type of dementia, is considered the third most costly disease in the USA, affecting patients primarily in long-term care nursing facilities (Makunts et al. 2019). It was reported that PPI administration had a significant increase in memory impairment adverse reaction outcomes compared to that of H2RA (H2 receptor antagonist) administration (Makunts et al. 2019). The memory impairment cohort included AD-type dementia, non-AD type dementia, memory impairment, and amnesia. There were zero reports of AD-type dementia in the H2RA administration group, and the PPI administration group had 80 reports (Makunts et al. 2019). Furthermore, this study observed higher risk association with PPI administration compared to H2RA administration in neuropathies, hearing impairment, visual impairment, and seizures (Makunts et al. 2019). The neuropathy cohort should be interpreted with caution as the PPI administration associated neuropathy could be secondary to vitamin B12 deficiency. Although rare, case reports of neuropathy due to PPI administration have been documented, namely omeprazole, but also lansoprazole (Rajabally and Jacob 2005). In this case study, the onset of neuropathic symptoms overlaying the time point of initiation of lansoprazole and the cessation of these clinical and electrophysiological symptoms after discontinuation of lansoprazole are suggestive of causation (Rajabally and Jacob 2005). Contrary to the findings of Makunts et al., hearing loss was hypothesized to be a cause of GERD and not PPI administration (Lin et al. 2017). However, if this were true, there should be less incidence of GERD related hearing loss in PPI administration groups, as PPIs offer greater gastric acid suppression compared to H2RA administration. Case studies in Bremen, Germany observed that in two separate patients administered PPIs for at least 5 weeks reported visual impairment accompanied by pain (Schonhofer et al. 1997). However, the causation of such outcomes stemmed from more of exclusion of other

Table 1 The common possible side effects of PPIs as well as the common possible side effects of long-term PPI use

Common possible side effects of PPIs	Common possible side effects of long-term use of PPIs
Headache	Lower respiratory tract infection
Gastrointestinal discomfort	Gastrointestinal infection
Constipation	Bacterial overgrowth
Allergic reaction	Changes in overall gut microbiome
Dizziness	Iron deficiency
	Bone fracture
	Vitamin B12 deficiency
	Magnesium deficiency
	Gastric cancer
	Colon cancer
	Hepatic encephalopathy
	Dementia
	Chronic kidney disease
	Acute interstitial nephritis
	Cardiovascular disease
	Allergic reaction
	Drug interactions

Lo and Chan (2013) and Rane et al. (2017)

possible diseases and not confirmatory methods of PPI causation. A study done with the German aging, cognition, and dementia databases found an increased risk for dementia in individuals using PPIs long-term compared to non-long-term PPI use (Haenisch et al. 2015). Additional studies are needed to further elucidate the exact mechanism of action as well as the frequency that PPIs can lead to dementia. However, it is predicted that PPIs may disrupt scavenger enzymes and their activity leading to increased beta amyloid amounts in the brain which has been shown to correlate with dementia progression (Jaynes and Kumar 2019). In both cell culture and mouse model studies, Lansoprazole, omeprazole, pantoprazole, and esomeprazole showed increases in amyloid beta concentrations, specifically amyloid beta 40 and 42 in a dose-dependent manner, (5 μM-50 μM) which is physiologically relevant (Badiola et al. 2013). Interestingly, multiple amyloid beta species are generated, with amyloid beta 40 being the most common, because γ-secretase has multiple amyloid precursor protein (APP) cleavage sites and can be impacted by small molecule drugs referred to as γ-secretase modulators. These modulators can shift the γ-secretase cleavage site, yielding different amyloid beta production patterns, where lansoprazole increased production of amyloid beta 42 (Badiola et al. 2013). Another study that investigated whether PPIs impacted the rate of Alzheimer's disease and non-Alzheimer's dementia found no correlation between PPIs and Alzheimer's disease. However, this study found a significant correlation between non-Alzheimer's dementia and the use of PPIs (Torres-Bondia et al. 2020). In addition, PPIs may have an impact on multiple pathways resulting in aberrant amyloid beta production as evidenced by PPI administration increasing beta-site amyloid precursor protein cleaving enzyme (BACE 1) activity, as well as possibly affecting proteases such as meprin β via variations in pH leading to increased production of amyloid beta (Badiola et al. 2013). Additionally, the degeneration of cholinergic neuronal networks is of the key features of AD, Down syndrome, Parkinson's disease dementia, and dementia with Lewy bodies. PPIs demonstrated high in silico scores against human choline acetyltransferase (chAT) where all tested PPIs demonstrated near complete inhibition of the enzyme activity of chat (Kumar et al. 2020). Omeprazole had a similar potency to that of the strong chAT inhibitor, α-NETA with esomeprazole and rabeprazole 2 and 5 times stronger, respectively (Kumar et al. 2020). Interestingly, the *in-silico* experiments illustrated that PPIs theoretically could pass through the blood brain barrier which has also been shown in the rat model as omeprazole was observed to rapidly diffuse into the striatum with omeprazole blood concentration declining in parallel leading to an equilibration between peripheral blood and brain (Cheng et al. 2002). In a meta-analysis study done including six cohort studies regarding the risk between PPI usage and dementia found no significant difference between PPI users and non-PPI users and the risk of dementia (Li et al. 2019). However, it should be noted that the relatively low number of studies may not be able to overcome biases. Furthermore, according to Li et al., the methods, inclusion criteria, study design, and study populations had large variability across the different studies included in the meta-analysis, which may induce difficulty in relating PPI usage and dementia (Li et al. 2019).

Cardiovascular disease in long-term PPI use

The long-term use of PPIs has been associated with cardiovascular events such as myocardial infarctions as well as strokes (Yibirin et al. 2021). There are also potential indirect associations due to nutrient deficiencies caused by the long-term use of PPIs. Therefore, multiple pathways are hypothesized as to how the long-term use of PPIs can cause cardiovascular events ranging from changes in nitric oxide levels, magnesium deficiencies, increases in chromogranin A, and effects on cytochrome P450 enzymes (Yibirin et al. 2021). Cardiovascular events caused by PPIs are mostly associated with high doses and long-term use. A study done with the average follow up time of around 6 years including 214,998 individuals showed an increased risk of ischemic stroke

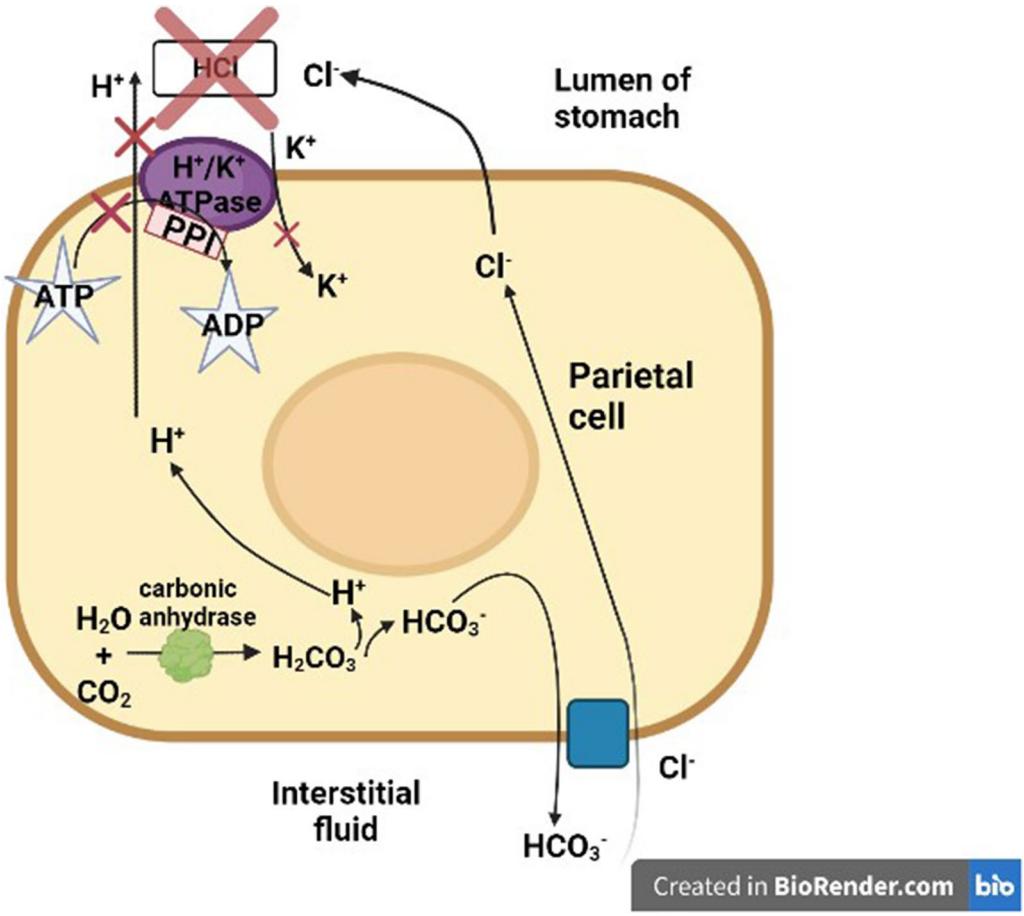

Fig. 2 Mechanism of action of proton pump inhibitors in a parietal cell. As hydrogen secretion is inhibited by PPIs, the subsequent formation of hydrochloric acid is thus inhibited as well resulting in an alkalization of the stomach contents

and myocardial infarctions accompanying long term PPI use (Sehested et al. 2018). The study defined short-term and long-term use of PPIs as less than 84 days or greater than 84 days after upper endoscopy, respectively. PPI use was associated with increased hazard ratios of 1.13 and 1.31 with p values less than 0.001 for ischemic stroke and myocardial infarction, respectively. High dose PPI use was significantly associated with the aforementioned hazard ratios. Interestingly, H2 receptor antagonists, which have a different mechanism of action but the same overall objective as PPIs, which is to lower the acidity of the stomach showed no significant association with ischemic stroke or myocardial infarction. These risks should be considered when prescribing and using PPIs especially if long-term use or high doses are warranted. Also, long-term PPI use in individuals who are at high risk of cardiovascular disease should be evaluated and monitored closely.

Nutrient deficiencies in long-term PPI use

Long-term PPI usage can have a negative impact on the absorption of a variety of important nutrients in the body. Hindrance of absorption of nutrients can lead to many health complications depending on the severity of the malabsorption state. Also, the absorption of certain nutrients can depend on the absorption of others, and if inhibited, could lead to additional malabsorption of nutrients indirectly related to long-term PPI usage. Some of the most studied nutrient abnormalities related to the long-term use of PPIs are hypomagnesemia, hypocalcemia, vitamin B12 deficiency, and hypo/hyperkalemia (Heidelbaugh 2013). Interestingly, paracellular permeability was altered during omeprazole treatment in colorectal adenocarcinoma cells (Caco-2). This was shown by a change in selectivity of ions in control cells ($P_{Na} > P_K > P_{Rb} > P_{Cs} > P_{Li}$) compared to 14 days omeprazole treated cells ($P_K > P_{Na} > P_{Rb} > P_{Cs} > P_{Li}$) (Thongon 2011). Omeprazole inhibited Caco-2 permeability to the monovalent cations discussed, in a dose-dependent response, illustrating that high doses can impact said ions

(Thongon 2011). It is important to note that not everyone will experience abnormalities related to long-term use of PPIs, but their use can possibly increase the risk of such deficiencies for example, in individuals where prior issues with nutrient absorption are already a factor. Hypomagnesemia usually presents with hypocalcemia and hypokalemia (Heidelbaugh 2013). Hypomagnesemia can lead to serious health conditions such as seizures and abnormal heart rhythms. Thus, it is imperative that the use of PPIs be regulated as to not induce such deficiencies. Importantly, urinary Mg^{2+} excretion is reduced, depicting compensation for reduced intestinal Mg^{2+} absorption, and excluding renal loss of Mg^{2+} as a cause for deficiency (Gommers et al. 2022). Also, it is important to note that supplementation of magnesium during PPI treatment had no effect on magnesium levels (Thongon 2011). PPI treatment would need to be stopped in order to restore magnesium levels if deficient. It is estimated that 30–50% of Mg^{2+} is absorbed in the intestines and this percentage may increase if there is deficiency present (Baaij et al. 2015). In the small intestine, Mg^{2+} absorption is predominantly mediated by the paracellular pathway, but is not well understood (Baaij et al. 2015). In Caco-2, the transport of Mg^{2+} from apical to basolateral was inhibited after 14 days of omeprazole treatment compared to the untreated group (Heidelbaugh 2013). This inhibition is hypothesized to be in a dose- and time-dependent manner as 21-day omeprazole treatment further decreased Mg^{2+} apical to basolateral transport compared to 14-day omeprazole treatment (Heidelbaugh 2013). The transient receptor potential melastatin (TRPM6/7) is responsible for the absorption of magnesium in the colon and can be inhibited or decreased in activity due to PPIs (Srinutta et al. 2019). This decrease in absorption is hypothesized to be caused via the alkalization of the colonic lumen, resulting in both decreased solubility of Mg^{2+} as well as the expression of the TRPM channels (Gommers et al. 2022). It is proposed that the suppression of gastric acid by PPIs also hinders the ability to solubilize calcium from food leading to lower absorption because of the change in pH (Yang 2012). Hypocalcemia can lead to changes in mental status and increased fractures due to weakening of the bones. Long-term use of PPIs can cause hypergastrinemia, which can impact the parathyroid leading to an increase loss of calcium from bone (Yang 2012). The parathyroid hormone (PTH) regulates calcium and bone metabolism by maintaining serum calcium levels, stimulating bone resorption, increasing renal tubular calcium reabsorption, and calcitriol production that is responsible for increasing active transport of calcium in the upper intestine (Yang 2012). PPIs cause a significant increase in gastrin via inhibition of somatostatin release from mucosal D cells which has shown to have stimulatory effects of the parathyroid gland evidenced by hypergastrinemia leading to increased parathyroid gland volume and weight in rats (Yang 2012). In humans, omeprazole therapy of eight weeks led to an increase of 28% in PTH levels (Yang 2012). Also, as previously mentioned, long-term use of PPIs can cause lower absorption of calcium. It is important to note that calcium sources such as milk and cheese have a higher bioavailability and therefore may be able to decrease calcium deficiencies if a regimen is followed. It has also been found that Omeprazole can decrease the ability to absorb calcium carbonate in elderly women (Jaynes and Kumar 2019). Due to the suppressed gastric acid secretion, vitamin B12 is not properly cleaved and as a result leads to decreased absorption. In the absence of gastric acid and not being properly cleaved, vitamin B12 cannot avoid pancreatic digestion leading to lower levels being absorbed (Thongon 2011). A deficiency in vitamin B12 can lead to altered mental status, weakness, anemia, and heart palpitations. Because of physiologic reserves of vitamin B12, much of the population would not experience vitamin B12 deficiency, but in populations where vitamin B12 intake is already hindered, PPIs should be used with caution. PPIs were shown to cause increases in serum potassium levels by suppressing adrenal cortical steroid synthesis (Gau et al. 2009). Hyperkalemia can lead to abnormal heart rhythms and muscle weakness, which can cause serious health complications. There have also been cases of patients with hypokalemia while undergoing PPI treatment, with increased urinary output of potassium. Hence, potassium levels may need to be measured in patients taking PPIs.

Gut dysbiosis caused by long-term PPI use

Perhaps the most intriguing side effect of long-term use of PPIs is the dysbiosis of the gastrointestinal microbes, which are critical for digestion/breakdown of dietary nutrients as well as protection from pathogens. The normal microbiota is in precise equilibrium with one another, and this balance is what promotes a healthy gut. If the balance in the microbiome is perturbed, there can be the initiation of intestinal and extra-intestinal diseases (Belizário et al. 2018). Dysbiosis can occur throughout the digestive tract, resulting from overgrowth or depletion of certain microbes. Importantly, the normal microbiota consists of multiple different variants of microbes that function together, whereas dysbiosis normally stems from the overgrowth of certain microbes leading to less overall variety in the microbiome. In long-term PPI treatments, it has been shown that the diversity of the microbiota is significantly reduced compared to that of the normal microbiota throughout the gastrointestinal tract (Bruno et al. 2019). The various parts of the digestive tract

have their own distinct normal microbiota that can be regulated by different factors such as pH, other microbes, environmental factors, and genetic factors. PPI use can also increase the risk of pathogenic microbial infections. This may occur because the probiotic microbes are lost due to the overgrowth of other microbes, or the alteration of the pH due to the suppression of gastric acid secretion may make it easier for pathogenic microbes to initiate infection. It has been documented that mostly gram-positive bacteria are found in healthy individuals' esophagus, whereas mostly gram-negative bacteria are found in unhealthy individuals' esophagus such as Barrett esophagus (Bruno et al. 2019). This change in the type of bacteria could lead to increased lipopolysaccharides (LPS) which may lead to inflammatory responses. The main locality of action for PPIs is the stomach, which is meant to increase the pH of the gastric fluid. This increase in pH can also alter the gut microbiota leading to H. pylori infections as well as overgrowth of other microbes. Table 2 illustrates how the microbiome may be effected by long-term PPI use. The more alkaline pH of the stomach caused by PPIs can also allow the survival of microbes normally eradicated by the stomach acid resulting in alteration of the subsequent microbial environments as well. Thus, it is proposed that SIBO results from the loss of the acidic barrier (Bruno et al. 2019). The colon can also experience changes in microbial flora due to PPIs. Interestingly, there have been reports of oral bacteria in the stool of patients prescribed PPIs (Bruno et al. 2019). In patients with Crohn's disease (CD) and ulcerative colitis (UC), higher amounts of *Escherichia coli* have been observed pointing to the possibility that administration of PPIs would further induce these infections (Bruno et al. 2019). Gut dysbiosis can also play a role in gastrointestinal cancers. It was found that the association of colorectal cancer increased with the use of PPIs and that the long-term use of PPIs further increased this association (Lei et al. 2021). However, the overall associated risk of colorectal cancer was low in PPI users and would need further investigation. It has also been shown that the gut microbiota in patients with colorectal cancer is significantly different from that of a healthy patient (Jobin 2013). There has also been evidence that points to the fact that changes in the microbiota can lead to the exacerbation of inflammation in inflammatory bowel disease (Reinink 2017). These ailments collectively further strengthen the evidence that the use of PPIs should be prescribed with caution and need to have clear indications of use to prevent the overuse of such drugs.

Infections and long-term use of PPIs

Due to PPIs irreversibly blocking the H^+/K^+ ATPase enzyme system, the long-term use of PPIs is known to chronically suppress gastric acid secretion leading to hypochlorhydria. Hypochlorhydria associated with PPI use has been hypothesized to be the root cause of small intestinal bacterial overgrowth (SIBO) by altering the intraluminal pH promoting dysbiosis of the bacterial flora in the small intestine (Lo and Chan 2013). SIBO is classified as the abnormal increase in the overall bacterial population of the small intestine, which may include species of bacteria not normally present in the small intestine. Lo and Chan also illustrated that in studies using glucose hydrogen breath test to diagnose SIBO, there was no significant association between PPI use and SIBO. When only using studies that involved duodenal/jejunal aspirates for SIBO diagnosis, a significant association between SIBO and PPI use was detected (Lo and Chan 2013). However, according to Giamarellos-Bourboulis et al., SIBO was independent of PPI use (Giamarellos-Bourboulis et al. 2016). Although this study also used aspirates from the duodenum, this particular study defined PPI use as administration of a PPI for at least a month on a daily basis prior to the study (Giamarellos-Bourboulis et al. 2016). Furthermore, in a study done to investigate the roles of PPIs and SIBO and their effects

Table 2 Bacteria families present in the gastroinestinal tract that are altered in at least two studies

Bacteria family	Bacterial population in response to PPIs
Enterococcaceae	Increased (Imhann et al. 2016); (cross sectional study 1815 subjects) (Freedberg et al. 2015); (12 healthy volunteers)
Lactobacillaceae	Increased (Imhann et al. 2016); (cross sectional study 1815 subjects) (Jackson et al. 2016); (cross sectional study 1827 subjects)
Micrococcaceae	Increased (Imhann et al. 2016); (cross sectional study 1815 subjects) (Jackson et al. 2016); (cross sectional study 1827 subjects) (Freedberg et al. 2015) (12 healthy volunteers)
Pasteurellaceae	Increased (Imhann et al. 2016); (cross sectional study 1815 subjects) (Jackson et al. 2016); (cross sectional study 1827 subjects)
Ruminococcaceae	Decreased (Imhann et al. 2016); (cross sectional study 1815 subjects) (Jackson et al. 2016); (cross sectional study 1827 subjects)
Staphylococcaceae	Increased (Imhann et al. 2016); (cross sectional study 1815 subjects) (Jackson et al. 2016); (cross sectional study 1827 subjects) (Freedberg et al. 2015) (12 healthy volunteers)
Streptococcaceae	Increased (Imhann et al. 2016); (cross sectional study 1815 subjects) (Jackson et al. 2016); (cross sectional study 1827 subjects) (Freedberg et al. 2015) (12 healthy volunteers)

on bile acid metabolism, patients taking PPI medication and having SIBO induced a reverse ratio of conjugated and unconjugated bile salts (1:3) when compared to patients using PPIs without SIBO (3:1) (Theisen 2000). This study also established that a gastric pH of 3.8 and below resulted in no bacterial overgrowth. However, a gastric pH of above 3.8, seen in PPI users, showed significant bacterial overgrowth of the small intestine (Theisen 2000). It is important to note that patients in this study were treated for GERD with 40 mg omeprazole for at least three months prior to sampling of gastric contents, while the control group, which also had symptoms of GERD similar to the experimental group, was restricted from utilizing acid-suppressing medications for at least two weeks prior to examination of gastric contents (Theisen 2000). According to Shindo et al., omeprazole treatment induced altered bile acid metabolism (Shindo et al. 1998). The study involved patients with gastric ulcer as well as healthy volunteers that were administered 20 mg omeprazole daily for five weeks. For both treatment groups, bacterial overgrowth was present in the stomach and jejunum where the bacteria found had deconjugation of bile acid capabilities, inducing fat malabsorption (Shindo et al. 1998). Altered bile acid metabolism is an important clinical finding as the imbalance of conjugated and unconjugated bile acids can lead to chronic diarrhea secondary to fat mal-digestion and absorption (Zaidel and Lin 2003). As the association between SIBO and altered bile acid metabolism is generally well accepted, there is still uncertainty of how conjugated and unconjugated bile acids specifically affect the host. Furthermore, the association between PPI use and SIBO has conflicting results from multiple studies. However, many of these studies used different analytical methods for the diagnosis of SIBO, for example the glucose hydrogen breath test compared to duodenum jejunal aspirates. The aspirate method is considered the gold standard of diagnosis (Lo and Chan 2013). Moreover, studies differ in what is considered long-term PPI use illustrated here by the different dosages and time frame. Therefore, more research is needed in order to better elucidate the association between PPI use and SIBO.

Clostridioides difficile infection with PPI use

As PPIs can induce changes in the gastrointestinal microbiome, these changes can also lead to a disruption in the gastrointestinal barrier which is thought to then allow the entry of pathogens past the barrier. This can lead to increased risk of infections which can range from mild to severe. *Clostridioides Difficile* (*C. difficile)* is a major bacterial infection that can often lead to hospitalization and is found to be increasing in number of infections. There are around 170,000 infections annually in the USA, not including nosocomial infections (https://www.mayoclinic.org/diseases-conditions/c-difficile/symptoms-causes/syc-20351691). Other enteric infections that can occur because of gut dysbiosis are *salmonella*, *Shigella*, and *Campylobacter* (Imhann et al. 2016). The exact mechanism of why these enteric infections occur is not known. However, it is thought that the alkalinity in the gastrointestinal tract caused by PPIs leads to the survival of pathogenic microbes that would otherwise not be able to survive the normal gastric acid and then leads to the colonization of these microbes in the gut microbiota. Along with this hypothesis, PPIs have been shown to increase bacterial species that are normally found in the mouth, such as *Rothia dentocariosa, Rothia mucilaginosa,* the genera *Actinomyces,* and the family *micrococcaceae* in the gut microbiota as well, which would correlate with the alkalinity of gastric acid as the cause of gut dysbiosis (Imhann et al. 2017). A study done to examine fecal pH and *C. difficile* infections found that 86.7% of individuals had both an alkaline fecal pH and were positive for *C. difficile* infection (Tawam et al. 2021). In a meta-analysis study, PPI use was associated with a significant increase in *Clostridiodes difficile* associated diarrhea (Janarthanan et al. 2012). This study showed no publication bias however, there was evidence of heterogeneity not explained by study design. Moreover, the dose of PPIs as well as the duration of use either differed between studies included or was not available for the studies, limiting the ability of the meta-analysis study to observe any further association between dose and duration of PPI therapy and *C. difficile* associated diarrhea. Another hypothesis is that the overgrowth of certain bacteria leads to changes in the nutrients present for the bacteria in the gut and may better support the growth of *C. difficile* as well as other known pathogenic bacteria. For example, colonic T regulatory cells, which can be enhanced by increased production of short chain fatty acids (SCFA), control inflammation by limiting the proliferation of effector $CD4^+$ T cells (Smith et al. 2013). The most prevalent SCFAs are propionate, acetate, and butyrate, where *Bacteroidetes* produce mainly acetate and propionate and *Firmicutes* mainly produce butyrate (Parada Venegas et al. 2019). Alterations in the gut microbiome associated with PPI use may alter the amount and ratio of bacteria species that produce SCFA. According to Lee et al., PPI administration decreased *Prevotella*, a genus of *Bacteroidetes* (Lee et al. 2019). This decrease may change the amount of production in SCFA overall resulting in decreased activation of colonic T regulatory cells possibly resulting increased inflammation. Elevated SCFA levels are also associated with lower levels of *C. difficile* infections as well as disease symptoms (Gregory et al. 2021). As additional studies are needed to further elucidate the

exact mechanism of why the enteric infections occur at a higher rate in PPI users, there is overwhelming evidence that PPI usage can impact the gut microbiota.

Long-term PPI use and pneumonia

There have also been studies evaluating the association of long-term PPI use and pneumonia which have also presented conflicting results. Multiple studies have illustrated that there is an increase in pneumonia incidence immediately before PPI use as well as after (Wang et al. 2022; Zirk-Sadowski et al. 2018). However, the interpretation differs as Pasternak et al. attributes this pattern of pneumonia association to underlying risk of pneumonia that is present around time of PPI administration independent of PPI use (Wang et al. 2022). Ble et al. interpret the increased risk of pneumonia immediately before and after PPI use as due to biases as well, but further demonstrate that an increased incidence of pneumonia was associated with long term PPI use present in the second year (Zirk-Sadowski et al. 2018). Both studies included any use of oral PPIs and used prescription data to indicate usage. Neither addressed dosage specifically. Interestingly Kao et al. report an association of increased risk of pneumonia and PPI use in Taiwan patients with type two diabetes mellitus (Lin et al. 2019). Pneumonia incidence was found to be 11.4% higher in PPI users than non-users in the type two diabetes mellitus cohort (30.3% vs. 18.9%) (Lin et al. 2019). There was also a dosage dependent increase in associative risk with pneumonia where higher dosage of PPIs was associated with increased risk of pneumonia (Lin et al. 2019).

Long-term PPI use and spontaneous bacterial peritonitis

Spontaneous bacterial peritonitis is a bacterial infection of the ascitic fluid common in cirrhotic patients with ascites (Dahabra et al. 2022). Not surprisingly, there have been conflicting reports of long-term PPI use and SBP. In a retrospective study, PPIs were associated with an increased risk of SBP in cirrhotic patients compared to SBP in non-PPI cirrhotic patients (3.3% vs. 0.76%) (Dahabra et al. 2022). PPI use was also associated with a higher odds ratio of 4.24 indicating a higher risk of SBP with PPI use (Dahabra et al. 2022). Further, a 2.5% incidence risk of SBP was associated with PPI use, whereas a national study in Taiwan defined the incidence of SBP in cirrhotic patients of around 0.1% (Boustany 2023). However, Reiberger et al. found similar rates of SBP in PPI vs non-PPI groups (19% vs 17% $p=0.691$) as well as no increase in odds ratio associated with PPI use (OR: 1.11 Cl 0.602–2.061 $p=0.731$) (Mandorfer et al. 2014). Thus, the rate of SBP could be contributed to severity of disease and other complications rather than directly to PPI use. Also, size of study and lack of control for confounding factors are common limitations of studies (Mandorfer et al. 2014). Nevertheless, pneumonia and SBP are both thought to stem from the inhibition of gastric acid and subsequent bacterial overgrowth (Dahabra et al. 2022).

Impact of PPI use in inflammatory bowel disease patients

IBD includes both CD and UC. These two diseases are thought of as two separate entities as they differ in clinical and pathologic identifiers but can both be referred to under the broad name of inflammatory bowel disease. These diseases can have a profound negative impact on the patient's quality of life and can also lead to morbidity as life-threatening complications can occur. In mouse studies that investigated PPI use and the resulting severity of experimental colitis, PPIs were found to increase the severity of experimental colitis, as well as illustrated a significant increase in weight loss and disease activity index scores (Nighot et al. 2022). This study defined the long-term physiologic dose of PPI as 20 mg/kg per day for 30 days (Nighot et al. 2022). Furthermore, the study illustrated that Caco-2 cells grown in alkaline media (pH 8.5) yielded an increase in myosin light chain kinase expression and activation when compared to control pH (7.3–7.6) leading to increased intestinal epithelial tight junction permeability. This in vitro alteration of tight junction permeability correlated with the mechanism of how PPI induced increase in tight junction permeability in vivo as PPI administration did not have a significant impact in mice lacking the myosin light chain kinase gene in the experimental colitis models (Nighot et al. 2022). In this same study, the long-term use of PPIs led to an increase in hospitalization rates of IBD patients, which included 45,151 matched adult patients (Nighot et al. 2022). These experimental data, as well as the retrospective chart review of PPI and non-PPI hospitalization rates of patients, suggest that long-term use of PPIs can have a profound impact on the various pathways implicated in IBD leading to more severe complications. Furthermore, in a study where 3 cohorts were analyzed (Nurses' Health Study (NHS) $n=82{,}269$; Nurses' Health Study 2 (NHS 2) $n=95{,}141$; and UK Biobank $n=469{,}397$) there was an association with increased risk of IBD in PPI users compared to non-PPI users (Xia et al. 2021). The study was designed to include participants taking PPIs and that were IBD and cancer free at the start of the study and then followed up with the participants 12 years later for the two NHS cohorts and 5 to 9 years for the UK Biobank cohort. PPI use in the NHS and NHS 2 cohorts was defined as taking a PPI 2 or more times a week. In the UK Biobank cohort, PPI regular use was defined as taking a PPI most days of the week for the last 4 weeks from time of questionnaire. This study also compared the use of PPI to H2 receptor antagonist, which is a less

potent acid suppressor than that of PPIs. This comparison allowed for the exclusion of potential confounding by underlying clinical indications such as GERD, gastric or duodenal ulcers, and gastrointestinal bleeding in the association of PPIs and IBD. When comparing the risk of IBD in PPI users and H2 receptor antagonists, PPI users were found to be associated with an increased risk of IBD (Xia et al. 2021). Furthermore, evidence also suggested that IBD patients undergoing treatment are less likely to achieve remission when concurrently under PPI treatment. In a study done of IBD treatment with Infliximab, a biologic drug, there was a significant association between decreased remission rates and PPI use. After propensity score matching, the remission rates were 30% for the PPI group and 49% for the non-PPI group at week 30 ($p < 0.001$) (Lu et al. 2021). This significance was only seen in CD and not UC according to this study. Patients using PPIs had an increase in hospitalizations compared to non-PPI users (15% and 8% $p = 0.007$) (Lu et al. 2021). Additionally, an association was found between PPI use and three IBD outcome measures; new biologic prescription (OR 1.11, 95% CI 1.04–1.18), IBD-related hospital admissions (OR 1.95, 95% CI 1.74–2.19), and IBD-related surgeries (OR 1.46, 95% CI 1.26–1.71) (Choden et al. 2023). The increased odds ratio for PPI associated IBD-related hospital admissions and IBD related surgeries was observed for both UC and CD, while new biologic prescription was only observed in patients with UC (Choden et al. 2023). Also, after propensity score matching, a significant association was observed between PPI use and all three measures (new biologic 23% vs 21% $p = 0.011$, IBD-related admission 8% vs 4% $p < 0.001$, IBD-related surgery 4% vs 2% $p < 0.001$) compared to PPI non-users (Choden et al. 2023). There was also a small but significant association between PPI dose and new biologic use (OR 1.03, 95% CI 1.02–1.04) and IBD-related admissions (OR 1.04, 95% CI 1.02–1.06) but not IBD-related surgery (Choden et al. 2023). It should also be noted that despite adjustment for confounders, causal relationships cannot be established and this study relies heavily on accuracy of claims and prescription data. The latter is important from the aspect that PPIs are often bought over-the-counter and may represent additional bias. PPIs also presented an association with pediatric IBD as the disease risk score was 3.6 (95% CI 1.1–11.7) for PPIs and 1.6 (95% CI 0.7–3.7) for H2RA (Schwartz et al. 2019). This study utilized H2RA as a control to compare PPI administration to as these medications have similar actions and prescription criteria. However, due to the small sample size ($n = 6$ for control and $n = 6$ for PPI) as well as possible misdiagnosis of IBD prior to the study, further investigation is warranted. These findings suggest that PPI use may increase the risk for IBD as well as may be associated with a decrease in the effectiveness of certain IBD treatments.

Kidney injury associated with PPI

As with other body systems and ailments possibly impacted by the long-term use of PPIs, kidney injury associated with PPI therapy is controversial. In a study investigating if there is an association of kidney injury in relation to current, recent, or past use of PPIs, the study found that current PPI users are associated with a higher risk of acute interstitial nephritis (OR 11.98 95% CI 9.11–15.47) compared to past (OR 1.68 95% CI 0.91–2.86) or recent PPI users (OR 4.28 95% CI 1.57–9.49) (Blank et al. 2014). The study also states that there was an increase in association of PPI and kidney injury as age increased (Blank et al. 2014). These results should be interpreted with caution as the confidence intervals were wide and may not be precise, as well as the study utilized a small number of cases. Another study that utilized medical health records found an association between PPI use and the risk of acute kidney injury after adjusting for confounding factors (OR 4.35 95% CI 3.14–6.04, $p < 0.0001$) as well as an association between PPI use and the risk of chronic kidney disease (OR 1.20 95% CI 1.12–1.28, $p < 0.0001$) (Hart et al. 2019). The significance of these findings remained after propensity matching (Hart et al. 2019). Conversely, it was found that, after adjusting for confounding factors, PPIs were not significantly associated with hazard of death with mortality survival estimates of 96.1, 96.3, and 98.0 for no medication, PPI, and H2RA, respectively (Cholin et al. 2021). Furthermore, different chronic kidney disease stages and PPI use was not significantly associated with mortality (PPI vs. no medication $p = 0.96$, $n = 24{,}607$) (Cholin et al. 2021). These heterogenous results stem from the lack of consistent study parameters. For example, baseline characteristics differed between study populations, exclusion criteria are variable, PPI users are generally considered "sicker", and these studies rely on the accuracy and completeness of medical records. Nevertheless, these studies should serve as an indication that there is need for more randomized studies investigating the association of kidney injury and long-term PPI use.

Conclusions

As the use of proton pump inhibitors is a common practice for a variety of ailments, the increasing amount of research suggests that the use of PPIs should be more carefully selected. Also, the length of PPI use is an important aspect to consider, and to lessen the risk of side effects, should be kept as short as possible to achieve the desired result. This, along with more strict requirements for indication of need for PPIs, as suggested by the AGA,

and periodic reevaluations of efficacy could possibly aid in prevention of PPI associated side effects. Further, changes to research methods such as a more standardized definition of long-term PPI use, more standardized exclusion of confounding factors, and increasing research that utilizes other methods of acid suppression such as H2Ras may aid in more accurate conclusions. Additional research is needed in order to investigate exactly how and what other organ systems might be affected by PPI usage as many studies often conflict in data results. For this reason, the results of the studies should be interpreted with caution when deciding on a treatment regimen. Even so, the cumulative and increasing studies that indicate mild to moderate health risks cannot be ignored. Additionally, the fact that withholding medication warranted would be morally and ethically wrong. This poses a large obstacle in the investigation of PPI use as most studies are forced to rely on retrospective studies or non-human models, which further increase the number of variables leading to an unclear illustration of the effect of PPIs. Moreover, PPI use in elderly individuals needs special precautions based on the fact that the elderly population represents a large proportion of the total patient population utilizing PPIs and may already have underlying health conditions that could be exacerbated with the use of PPIs. With further improved investigations, clinicians would be better equipped to make a more accurate decision of how and when to prescribe PPIs and would be better able to treat PPI-induced health complications if they occur.

Abbreviations

PPI	Proton pump inhibitor
GERD	Gastroesophageal reflux disease
H^+/K^+ ATPase pump	Hydrogen/potassium ATPase pump
AGA	American Gastroenterological Association
IBD	Inflammatory bowel disease
BPAs	Best practice advice
HCl	Hydrogen chloride
AD	Alzheimer disease
H2RA	H2 receptor antagonist
APP	Amyloid precursor protein
BACE 1	Beta-site amyloid precursor protein cleaving enzyme
chAT	Human choline acetyltransferase
Caco-2	Colorectal adenocarcinoma cells
TRPM6/7	Transient receptor potential melastatin
PTH	Parathyroid hormone
SIBO	Small intestinal bacterial overgrowth
LPS	Spontaneous bacterial peritonitis-SBP lipopolysaccharides
CD	Crohn's disease
UC	Ulcerative colitis
C. difficile	*Clostridioides difficile*
SCFA	Short chain fatty acids

Acknowledgements
The authors would like to thank and recognize the Crohn's & Colitis Foundation Award 694583 [MN], as well as Dr. Prashant Nighot, Kushal Saha, Alexandra Wang, and Shannon Dalessio for editing contributions.

Author contributions
NM and MN contributed to the idea and conceptualization. Supervision and mentoring were performed by MN. Literature search and analysis were performed by NM. All drafts were written by NM. Editing and revisions were done by MN and supported by NM. MN and NM approved the final manuscript.

Funding
Not applicable.

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
No competing interests, financial or otherwise, are declared by the author[s].

Received: 19 July 2023 Accepted: 26 August 2023
Published online: 04 September 2023

References

Badiola N, Alcalde V, Pujol A et al (2013) The proton-pump inhibitor lansoprazole enhances amyloid beta production. PLoS ONE 8(3):e58837. https://doi.org/10.1371/journal.pone.0058837

Belizário JE, Faintuch J, Garay-Malpartida M (2018) Gut microbiome dysbiosis and immunometabolism: new frontiers for treatment of metabolic diseases. Mediators Inflamm 2018:1–12. https://doi.org/10.1155/2018/203783831

Blank ML, Parkin L, Paul C, Herbison P (2014) A nationwide nested case-control study indicates an increased risk of acute interstitial nephritis with proton pump inhibitor use. Kidney Int 86(4):837–844. https://doi.org/10.1038/ki.2014.74

Boustany A (2023) Cirrhotic patients on proton pump inhibitors are at a twofold risk of spontaneous bacterial peritonitis independently of gastrointestinal bleeding: a population-based retrospective study. Ann Gastroenterol. https://doi.org/10.20524/aog.2023.0794

Bruno G, Zaccari P, Rocco G et al (2019) Proton pump inhibitors and dysbiosis: current knowledge and aspects to be clarified. WJG 25(22):2706–2719. https://doi.org/10.3748/wjg.v25.i22.2706

Cheng FC, Ho YF, Hung LC, Chen CF, Tsai TH (2002) Determination and pharmacokinetic profile of omeprazole in rat blood, brain and bile by microdialysis and high-performance liquid chromatography. J Chromatogr A 949(1–2):35–42. https://doi.org/10.1016/S0021-9673(01)01225-0

Choden T, Zhang H, Sakuraba A (2023) Influence of proton pump inhibitor use on clinical outcomes of patients with inflammatory bowel disease. Ann Med 55(1):2198775. https://doi.org/10.1080/07853890.2023.2198775

Cholin L, Ashour T, Mehdi A et al (2021) Proton-pump inhibitor vs. H2-receptor blocker use and overall risk of CKD progression. BMC Nephrol 22(1):264. https://doi.org/10.1186/s12882-021-02449-0

C. Difficile Infection. Mayo Clinic https://www.mayoclinic.org/diseases-conditions/c-difficile/symptoms-causes/syc-20351691

Dahabra L, Kreidieh M, Abureesh M, Abou Yassine A, Deeb L (2022) Proton pump inhibitors use and increased risk of spontaneous bacterial peritonitis in cirrhotic patients: a retrospective cohort analysis. Gastroenterol Res 15(4):180–187. https://doi.org/10.14740/gr1545

de Baaij JHF, Hoenderop JGJ, Bindels RJM (2015) Magnesium in man: implications for health and disease. Physiol Rev 95(1):1–46. https://doi.org/10.1152/physrev.00012.2014

Freedberg DE, Toussaint NC, Chen SP et al (2015) Proton pump inhibitors alter specific taxa in the human gastrointestinal microbiome: a crossover trial.

Gastroenterology 149(4):883-885.e9. https://doi.org/10.1053/j.gastro.2015.06.043
Gau JT, Heh V, Acharya U, Yang YX, Kao TC (2009) Uses of proton pump inhibitors and serum potassium levels: proton pump inhibitor and serum potassium level. Pharmacoepidem Drug Safe 18(9):865–871. https://doi.org/10.1002/pds.1795
Giamarellos-Bourboulis EJ, Pyleris E, Barbatzas C, Pistiki A, Pimentel M (2016) Small intestinal bacterial overgrowth is associated with irritable bowel syndrome and is independent of proton pump inhibitor usage. BMC Gastroenterol 16(1):67. https://doi.org/10.1186/s12876-016-0484-6
Gommers LMM, Hoenderop JGJ, de Baaij JHF (2022) Mechanisms of proton pump inhibitor-induced hypomagnesemia. Acta Physiol 235:4. https://doi.org/10.1111/apha.13846
Gregory AL, Pensinger DA, Hryckowian AJ (2021) A short chain fatty acid–centric view of clostridioides difficile pathogenesis. PLoS Pathog 17(10):e1009959. https://doi.org/10.1371/journal.ppat.1009959
Haenisch B, von Holt K, Wiese B et al (2015) Risk of dementia in elderly patients with the use of proton pump inhibitors. Eur Arch Psychiatry Clin Neurosci 265(5):419–428. https://doi.org/10.1007/s00406-014-0554-0
Hart E, Dunn TE, Feuerstein S, Jacobs DM (2019) Proton pump inhibitors and risk of acute and chronic kidney disease: a retrospective cohort study. Pharmacotherapy 39(4):443–453. https://doi.org/10.1002/phar.2235
Hayes KN, Nakhla NR, Tadrous M (2019) Further evidence to monitor long-term proton pump inhibitor use. JAMA Netw Open 2(11):e1916184. https://doi.org/10.1001/jamanetworkopen.2019.16184
Heidelbaugh JJ (2013) Proton pump inhibitors and risk of vitamin and mineral deficiency: evidence and clinical implications. Therap Adv Drug Saf 4(3):125–133. https://doi.org/10.1177/2042098613482484
Imhann F, Bonder MJ, Vich Vila A et al (2016) Proton pump inhibitors affect the gut microbiome. Gut 65(5):740–748. https://doi.org/10.1136/gutjnl-2015-310376
Imhann F, Vich Vila A, Bonder MJ et al (2017) The influence of proton pump inhibitors and other commonly used medication on the gut microbiota. Gut Microb 8(4):351–358. https://doi.org/10.1080/19490976.2017.1284732
Jackson MA, Goodrich JK, Maxan ME et al (2016) Proton pump inhibitors alter the composition of the gut microbiota. Gut 65(5):749–756. https://doi.org/10.1136/gutjnl-2015-310861
Janarthanan S, Ditah I, Adler DG, Ehrinpreis MN (2012) Clostridium difficile-associated diarrhea and proton pump inhibitor therapy: a meta-analysis. Am J Gastroenterol 107(7):1001–1010. https://doi.org/10.1038/ajg.2012.179
Jaynes M, Kumar AB (2019) The risks of long-term use of proton pump inhibitors: a critical review. Therap Adv Drug Saf 10:204209861880992. https://doi.org/10.1177/2042098618809927
Jobin C (2013) Colorectal cancer: looking for answers in the microbiota. Cancer Discov 3(4):384–387. https://doi.org/10.1158/2159-8290.CD-13-0042
Kinoshita Y, Ishimura N, Ishihara S (2018) Advantages and disadvantages of long-term proton pump inhibitor use. J Neurogastroenterol Motil 24(2):182–196. https://doi.org/10.5056/jnm18001
Kumar R, Kumar A, Nordberg A, Långström B, Darreh-Shori T (2020) Proton pump inhibitors act with unprecedented potencies as inhibitors of the acetylcholine biosynthesizing enzyme—a plausible missing link for their association with incidence of dementia. Alzheimer's Dementia 16(7):1031–1042. https://doi.org/10.1002/alz.12113
Lee SM, Kim N, Nam RH et al (2019) Gut microbiota and butyrate level changes associated with the long-term administration of proton pump inhibitors to old rats. Sci Rep 9(1):6626. https://doi.org/10.1038/s41598-019-43112-x
Lei WY, Wang JH, Yi CH et al (2021) Association between use of proton pump inhibitors and colorectal cancer: a nationwide population-based study. Clin Res Hepatol Gastroenterol 45(1):101397. https://doi.org/10.1016/j.clinre.2020.02.017
Li M, Luo Z, Yu S, Tang Z (2019) Proton pump inhibitor use and risk of dementia: systematic review and meta-analysis. Medicine 98(7):e14422. https://doi.org/10.1097/MD.0000000000014422
Lin BM, Curhan SG, Wang M et al (2017) Prospective study of gastroesophageal reflux, use of proton pump inhibitors and H2-receptor antagonists, and risk of hearing loss. Ear Hear 38(1):21–27. https://doi.org/10.1097/AUD.0000000000000347
Lin W-L, Muo C-S, Lin W-C, Hsieh Y-W, Kao C-H (2019) Association of increased risk of pneumonia and using proton pump inhibitors in patients with type II diabetes mellitus. Dose-Response 17(2):155932581984338. https://doi.org/10.1177/1559325819843383
Lo W, Chan WW (2013) Proton pump inhibitor use and the risk of small intestinal bacterial overgrowth: a meta-analysis. Clin Gastroenterol Hepatol 11(5):483–490. https://doi.org/10.1016/j.cgh.2012.12.011
Lu TX, Dapas M, Lin E, Peters T, Sakuraba A (2021) The influence of proton pump inhibitor therapy on the outcome of infliximab therapy in inflammatory bowel disease: a patient-level meta-analysis of randomised controlled studies. Gut 70(11):2076–2084. https://doi.org/10.1136/gutjnl-2020-321609
Makunts T, Alpatty S, Lee KC, Atayee RS, Abagyan R (2019) Proton-pump inhibitor use is associated with a broad spectrum of neurological adverse events including impaired hearing, vision, and memory. Sci Rep 9(1):17280. https://doi.org/10.1038/s41598-019-53622-3
Mandorfer M, Bota S, Schwabl P, Bucsics T, Pfisterer N, Summereder C, Hagmann M, Blacky A, Ferlitsch A, Sieghart W, Trauner M, Peck-Radosavljevic M, Reiberger T (2014) Proton pump inhibitor intake neither predisposes to spontaneous bacterial peritonitis or other infections nor increases mortality in patients with cirrhosis and ascites. PLoS ONE 9(11):e110503. https://doi.org/10.1371/journal.pone.0110503
Mullin JM, Gabello M, Murray LJ et al (2009) Proton pump inhibitors: actions and reactions. Drug Discov Today 14(13–14):647–660. https://doi.org/10.1016/j.drudis.2009.03.014
Nighot M, Liao PL, Morris N et al (2022) Long term use of proton pump inhibitor disrupts intestinal tight junction barrier and exaggerates experimental colitis. J Crohn's Colitis. https://doi.org/10.1093/ecco-jcc/jjac168
Parada Venegas D, De la Fuente MK, Landskron G et al (2019) Short chain fatty acids (SCFAs)-mediated gut epithelial and immune regulation and its relevance for inflammatory bowel diseases. Front Immunol 10:277. https://doi.org/10.3389/fimmu.2019.00277
Rajabally YA, Jacob S (2005) Neuropathy associated with lansoprazole treatment. Muscle Nerve 31(1):124–125. https://doi.org/10.1002/mus.20155
Rane PP, Guha S, Chatterjee S, Aparasu RR (2017) Prevalence and predictors of non-evidence based proton pump inhibitor use among elderly nursing home residents in the US. Res Social Adm Pharm 13(2):358–363. https://doi.org/10.1016/j.sapharm.2016.02.012
Reinink AR (2017) Do acid-suppressing medications in inflammatory bowel disease increase risk for flare? Digestion 95(3):186–187. https://doi.org/10.1159/000464283
Sarnaik MK, Modi S, Pisipati Y et al (2021) Proton pump inhibitors: exploring cardiovascular complications and prescription protocol. Cureus. https://doi.org/10.7759/cureus.16744
Schonhofer PS, Werner B, Troger U (1997) Drug points: ocular damage associated with proton pump inhibitors. BMJ 314(7097):1805–1805. https://doi.org/10.1136/bmj.314.7097.1805
Schwartz NRM, Hutfless S, Herrinton LJ et al (2019) Proton pump inhibitors, H2 blocker use, and risk of inflammatory bowel disease in children. J Pediatr Pharmacol Ther 24(6):489–496. https://doi.org/10.5863/1551-6776-24.6.489
Sean K. Omeprazole drug usage statistics, United States, 2013–2020. https://clincalc.com/DrugStats/Drugs/Omeprazole
Sehested TSG, Gerds TA, Fosbøl EL et al (2018) Long-term use of proton pump inhibitors, dose-response relationship and associated risk of ischemic stroke and myocardial infarction. J Intern Med 283(3):268–281. https://doi.org/10.1111/joim.12698
Shin JM, Sachs G (2008) Pharmacology of proton pump inhibitors. Curr Gastroenterol Rep 10(6):528–534. https://doi.org/10.1007/s11894-008-0098-4
Shindo K, Machida M, Fukumura M, Koide K, Yamazaki R (1998) Omeprazole induces altered bile acid metabolism. Gut 42(2):266–271. https://doi.org/10.1136/gut.42.2.266
Smith PM, Howitt MR, Panikov N et al (2013) The microbial metabolites, short-chain fatty acids, regulate colonic t reg cell homeostasis. Science 341(6145):569–573. https://doi.org/10.1126/science.1241165
Srinutta T, Chewcharat A, Takkavatakarn K et al (2019) Proton pump inhibitors and hypomagnesemia: a meta-analysis of observational studies. Medicine 98(44):e17788. https://doi.org/10.1097/MD.0000000000017788
Sun L, Zhang X, Zhang Y et al (2019) Antibiotic-induced disruption of gut microbiota alters local metabolomes and immune responses. Front Cell Infect Microbiol 9:99. https://doi.org/10.3389/fcimb.2019.00099

Targownik LE, Fisher DA, Saini SD (2022) AGA clinical practice update on deprescribing of proton pump inhibitors: expert review. Gastroenterology 162(4):1334–1342. https://doi.org/10.1053/j.gastro.2021.12.247
Tawam D, Baladi M, Jungsuwadee P, Earl G, Han J (2021) The positive association between proton pump inhibitors and clostridium difficile infection. Innov Pharm 12(1):21. https://doi.org/10.24926/iip.v12i1.3439
Theisen J (2000) Suppression of gastric acid secretion in patients with gastroesophageal reflux disease results in gastric bacterial overgrowth and deconjugation of bile acids. J Gastrointest Surg 4(1):50–54. https://doi.org/10.1016/S1091-255X(00)80032-3
Thongon N (2011) Omeprazole decreases magnesium transport across Caco-2 monolayers. WJG 17(12):1574. https://doi.org/10.3748/wjg.v17.i12.1574
Torres-Bondia F, Dakterzada F, Galván L et al (2020) Proton pump inhibitors and the risk of Alzheimer's disease and non-Alzheimer's dementias. Sci Rep 10(1):21046. https://doi.org/10.1038/s41598-020-78199-0
Wang Y-H, Svanström H, Wintzell V, Ludvigsson JF, Pasternak B (2022) Association between proton pump inhibitor use and risk of pneumonia in children: nationwide self-controlled case series study in Sweden. BMJ Open 12(4):e060771. https://doi.org/10.1136/bmjopen-2022-060771
Xia B, Yang M, Nguyen LH et al (2021) Regular use of proton pump inhibitor and the risk of inflammatory bowel disease: pooled analysis of 3 prospective cohorts. Gastroenterology 161(6):1842-1852.e10. https://doi.org/10.1053/j.gastro.2021.08.005
Yang YX (2012) Chronic proton pump inihibitor therapy and calcium metabolism. Curr Gastroenterol Rep 14(6):473–479. https://doi.org/10.1007/s11894-012-0290-4
Yibirin M, De Oliveira D, Valera R, Plitt AE, Lutgen S (2021) Adverse effects associated with proton pump inhibitor use. Cureus. Published online January 18. https://doi.org/10.7759/cureus.12759
Zaidel O, Lin HC (2003) Uninvited guests: the impact of small intestinal bacterial overgrowth on nutritional status. Pract Gastroenterol 27:27–33
Zirk-Sadowski J, Masoli JA, Delgado J, Hamilton W, Strain WD, Henley W, Melzer D, Ble A (2018) Proton-pump inhibitors and long-term risk of community-acquired pneumonia in older adults. J Am Geriatr Soc 66(7):1332–1338

Publisher's Note