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Review Article

An Update On Proton-Pump Inhibitors As A Treatment Of Peptic Ulcers And Gastroesophageal Reflux Disease (Gerd)

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ABSTRACT

Proton pump inhibitors (PPIs) are a class of drugs commonly used to treat a range of conditions that involve excess stomach acid production. In recent years, there have been several updates regarding the use of PPIs in these conditions. In this review article, we provide an overview of the mechanism of action of PPIs, their clinical efficacy and safety, and their use in the treatment of GERD. We discuss evidence supporting the use of PPIs in the management of GERD, as well as their potential side effects and risks. We also explore alternative treatment options for GERD and highlight the importance of lifestyle modifications in managing this condition. Overall, this review article aims to provide a comprehensive update on the use of PPIs in the treatment of GERD, offering insights and guidance for healthcare providers in the management of this common condition. We talk about the possible risk of long-term PPI usage, including an elevated risk of infections and bone fractures, and the ongoing debate about the appropriate duration of PPI therapy for GERD. Overall, PPIs are an important treatment option for patients with GERD, offering significant symptom relief and promoting the healing of oesophageal erosions. However, their long-term use should be carefully considered, and alternative treatment options should be explored when appropriate. Close monitoring and regular follow-up are important for patients taking PPIs to ensure optimal outcomes and minimize potential risks.

INTRODUCTION

Peptic ulcers and gastroesophageal reflux disease are prevalent conditions for which patients seek medical attention. When used to treat acid-related symptoms, antacids work quickly but only temporarily. H2RAs restrict the release of stomach acid but because they don't stop the hormones' stimulatory effects on acid production, their effects can fade over time. To control the discharge of stomach acid more effectively, PPIs, or proton pump inhibitors, were created [1].

The most typical gastroenterological outpatient diagnosis in the United States is gastroesophageal reflux disease (GERD), which has an annual

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incidence of 0.38 to 0.45 per cent in the Western world and a prevalence rate of 10 percent to 20 percent [2]. In the US, 7% of persons with GERD experience symptoms every day, while 20% experience symptoms at least once per week [3,4]. GERD significantly reduces the quality of life-related to health and costs the healthcare system a tonne of money [5].

When GERD is suspected, the majority of questions and concerns about the therapeutic strategy surface. After being initially proved to be superior to H2 receptor antagonists or sucralfate, the commercial dose of omeprazole (20 mg/day) swiftly emerged as the gold standard of treatment. The recommended doses of lansoprazole (30 mg/day), pantoprazole (40 mg/day), and rabeprazole (20 mg/day) were later used to collect equivalent data. The recommended doses of lansoprazole (30 mg/day), pantoprazole (40 mg/day), and rabeprazole (20 mg/day) were later used to collect equivalent data. However, it was soon found that a considerable number of patients either did not completely heal their lesions or remained to have clinically significant symptoms. It's interesting to note that in people without lesions, symptoms can occasionally be more difficult to control [6].

A modified pyridine and a benzimidazole are the two elements that makeup proton pump inhibitors (PPIs), which have weak bases (pKa 4.0–5.0) that are lipophilic. Sulfenic acids or sulfenamides, are produced when prodrugs are broken down. These sulfenamides or sulfenic acids are used to make PPIs. Esomeprazole, omeprazole, pantoprazole, lansoprazole, rabeprazole, ilaprazole, and dexlansoprazole are just a few examples of the proton pump inhibitors that are offered for sale. Despite having fundamentally similar structures, these PPIs vary in their pharmacokinetic and pharmacodynamic properties [7].

GERD, Zollinger-Ellison syndrome, dyspepsia, Helicobacter pylori infection, and peptic ulcer disease are only a few of the gastrointestinal conditions that are commonly treated with PPIs in clinical practice [8–12].

HISTORICAL BACKGROUND

Cimetidine, a competitive H2-receptor antagonist, was first introduced in 1976 and was the first antisecretory medication approved for the treatment of peptic ulcers and GERD [13,14](Figure 1). Its purpose was to keep parietal cells from becoming activated in a paracrine manner [15].

Soon it became clear that H2-receptor blockers effectively reduced the amount of stomach acid produced at rest but could Parietal cell secretion after meals is only partially stopped [16,17]. During that same year, it had been found a critical step in the parietal cells' process of secreting stomach acid is the H+/K+ proton pump, which depends on ATP. It has been found that inhibiting the proton pump is more efficient than suppressing the paracrine receptors that induce the secretion of acid [18]. In parietal cells, the newly created benzimidazole derivatives timoprazole and picoprazole directly blocked H+/K+-ATPase, it was found two years later, in 1978. These drugs had considerable antisecretory activity [13,19]. Timoprazole and picoprazole were discovered to be hazardous for both the thyroid and blood vessels, as further research on them indicates. The benzimidazole structure needed to be optimized as a result. Picoprazole was subsequently converted into omeprazole after substituents were added to the pyridine ring, increasing its pKa value [13].

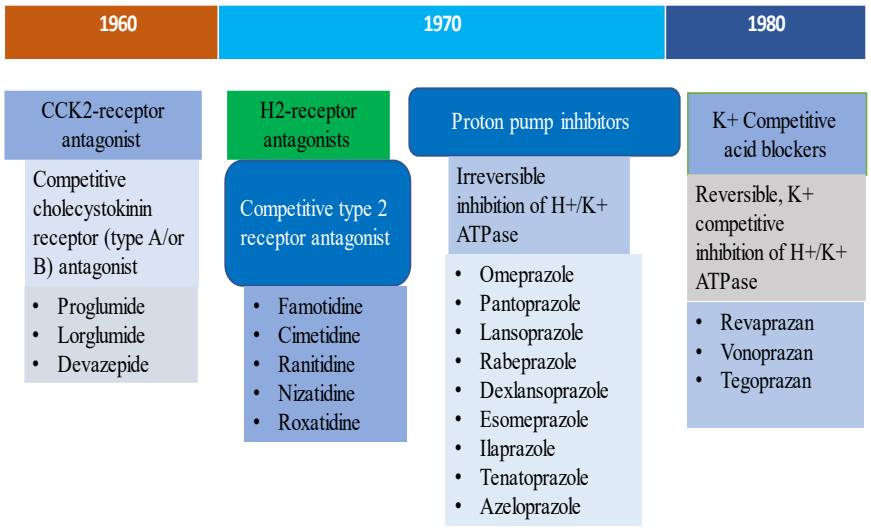

Fig 1. Antisecretory drugs [13,14,18,20–27].

GASTROESOPHAGEAL REFLUX DISEASE

In 2006, the Montreal Consensus Group established the term "gastroesophageal reflux disease" (GERD).as "a condition that occurs when the reflux of stomach contents [into the oesophagus] causes bothersome symptoms and/or problems" [28].

Heartburn and acid regurgitation, along with or without oesophageal mucosal injury, are symptoms of the prevalent illness known as gastroesophageal reflux disease (GERD) [29].

Due to the chronic nature of GERD, the majority of patients who stop taking their PPI prescription see a return of their symptoms. As a result, many GERD patients need to take PPIs on a long-term basis [30,31].

In addition, extra-oesophageal issues including chest pain and the emergence of asthma-like symptoms can be brought on by GERD [32]. Reports state that 19 million people in the US alone suffer from GERD. This number is probably under-representative because so many people have inaccurate diagnoses and hence receive subpar care [33]. Patients with these conditions report a worse standard of living than people who have diabetes, hypertension, moderate heart failure, angina, or GERD [34–36].

According to 2005 practice guidelines, acid suppression is the cornerstone of treatment for GERD [37] Over the past 30 years, a greater variety of drugs have been developed to regulate acid secretion and, consequently, GERD symptoms. Since the early 1970s, when the proton pump was discovered and proton pump inhibitors (PPIs) were created, the way that GERD is treated has undergone a revolution [38]. The initial PPI to treat GERD was omeprazole, which was released onto the market in 1989 [39]. Pantoprazole, the fourth PPI commercially accessible available in the US, was introduced in 2000. became the first PPI to be offered both orally and intravenously (iv) [40].

The current cornerstone of GERD treatment is acid regulation, particularly with proton pump inhibitors (PPIs). The inability of PPI therapy to reduce GERD symptoms has been the most typical GERD presentation in the last ten years of gastroenterology practice. Additionally, long-term

maintenance therapy with anti-reflux medications is typically required because GERD is a persistent, recurring condition. However, Neither the GERD medications that are now available on the market promise long-term recovery [41].

Post-prandially, gastroesophageal reflux disease (GERD), a usual physiological occurrence in such circumstances, affects almost everyone. On the other hand, it is referred to as gastroesophageal reflux disease when it happens often and either results in painful symptoms or harms the mucosa of the oesophagus (GERD) [42]. It might cause additional problems or, in certain cases, affect extra-oesophageal organs [43]. The concurrent disorders of esophagogastric dysmotility, oesophageal anatomic anomalies (such as tracheoesophageal fistula or developmental delay), and others can cause GERD even though it may happen even if there are no underlying risk factors [44].

The development of the antisecretory medication cimetidine, an antagonist of the histamine 2 (H2) receptor, one of the primary channels leading to gastric acid production, contributed to advancements in the medical management of acid-related disorders, including peptic ulcers and GERD. However, H2-receptor antagonists only have a transient effect [13].

OVERVIEW OF PROTON PUMP INHIBITORS

Proton pump inhibitors (PPIs), initially discovered in the late 20th century, lower stomach acids and have significantly improved the treatment of gastrointestinal illnesses [45]. Since then, it has been shown that PPIs are the first-line treatment for peptic ulcers, lowering the risk of rebleeding following endoscopy for high-risk acute peptic ulcers, as well as reducing the symptoms of gastroesophageal reflux disease and preventing complications (GERD) [46–49].

With yearly spending estimated at $13.5 billion in the United States and $24 billion globally in 2009, proton pump inhibitors (PPIs) have grown to be one of the most frequently prescribed medicine families [50].

The treatment of illnesses brought on by too much acid depends on proton pump inhibitors. In situations of gastro-oesophageal reflux disease (GERD), peptic ulcer disease, the eradication of Helicobacter pylori when combined with one or more antibiotics, such as stomach-protective agents while taking nonsteroidal anti-inflammatory drugs, these are the prescribed medications. Antacids and histamine-2-receptor antagonists were utilised to treat conditions brought on by excess acid before proton pump inhibitors were developed. Proton pump inhibitors are more effective than antacids and histamine-2-receptor antagonists in treating disorders associated with excess acid [51,52].

Proton pump inhibitors cause a considerable reduction in stomach acid production that lasts longer than the time when their plasma concentration is present. Due to irreversible inhibition, the pump must be created from scratch to restart the H+/K+-ATPase's activity [53]. Rebound hypersecretion is occasionally seen in patients with Helicobacter pylori (H. pylori) positive after proton pump inhibitor therapy has been discontinued, although it is uncommon [54]. For lowering stomach acid, proton pump inhibitors are more effective than histamine H2 receptor antagonists, in reducing pain, and healing oesophageal lesions, gastric ulcers, and duodenal ulcers, according to comparative research [55–57].

Mechanism of action of proton pump inhibitor-

The action of PPIs involves the adenosine triphosphatase (H+, K+-ATPase) pumps, which regulate stomach pH and lower the quantity of gastric acid produced as a result. The selective and irreversible binding of proton pumps, also known as H+, K+-ATPase pumps, by PPIs limits the formation of stomach acid at both its basal and stimulated levels. The effect of PPIs on acid

secretion is dose-dependent and the maximal effect is reached after several days of treatment. PPIs are therefore recommended for long-term use in the treatment of GERD [58].

Pharmacodynamics and pharmacokinetics of proton pump inhibitor-

It has been found that proton pump inhibitors work very well at lowering stomach acid production. They have the same mode of action even if their chemical structures are slightly different. It has been found that proton pump inhibitors work very well at lowering stomach acid production. They have the same mode of action even if their chemical structures are slightly different [59]. The H+/K+-ATPase enzyme, also known as the gastric proton pump and found in the parietal cells of the stomach, is inhibited by PPIs. The proton pump's function is to regularly release acid into the gastric lumen or to respond to outside stimuli like hormones, peptides, or neurotransmitters [60].

To reduce the proton pump's ability to function, inactive chemicals known as proton pump inhibitors must be activated in the parietal cells' acidic environment. Sometimes, although incorrectly, they are referred to as "prodrugs" [61]. More parietal cells accumulate, and the protonation process begins more quickly in PPIs with higher pKa values [61–64]. The biotransformed substances create disulfide bridges by creating covalent bonds with cysteine residues in the proton pump's subunit [63,65].

PPIs have a wide range of peak plasma drug concentrations based on the pace of passage in the gastrointestinal system, drug release, and intraduodenal PH [66]. PPIs take almost 3 days to completely suppress stomach acid and take some time to reach steady state inhibition of gastric acid [67].

Classification of PPIs-

The USFDA has approved six PPIs as of 2015 [68].(Table 1)

Table 1. Proton pump inhibitors with a commercial presence in the US

S.no	Drug	Dosages, (mg)	Generic	Intravenous	Suspension or liquid
1	Esomeprazole	20, 40	Yes	Yes	Yes
2	Omeprazole	10, 20, 40	Yes	Yes	No
3	Pantoprazole	20, 40	Yes	Yes	Yes
4	Rabeprazole	20	Yes	No	No
5	Lansoprazole	15, 30	Yes	Yes	Yes
6	Dexlansoprazole	30, 60	No	No	No

H2-RECEPTOR ANTAGONISTS

Over the past 20 years, cimetidine, ranitidine, famotidine, and nizatidine have all been utilised on a global scale. Roxatidine has also been commercialised in several regions. These specific antagonists suppress acid secretion by competitively and irreversibly blocking the basolateral membrane H2-receptors. The pharmacological properties of the drugs are quite similar, yet there are only minor structural changes. H2RAs are less effective at reducing intragastric acidity when basal acid secretion is taking place, and they only partially suppress gastrin-stimulated acid secretion [69,70].

PPI COMMON CLINICAL APPLICATIONS

Intravenously or orally, PPIs are administered. They are employed in the treatment of gastrointestinal conditions like:

- Healing of PUD
- Peptic ulcer-related gastrointestinal bleeding
- Eradication of H. pylori infection
- Zollinger-Ellison syndrome
- NSAID-induced gastroduodenal ulcer prevention.

- Gastroesophageal Reflux Disease (GERD)
- Duodenal and Gastric ulcers
- Erosive esophagitis
- Non-erosive reflux disease
- Functional dyspepsia [59].

Antisecretory action is a characteristic that proton pump inhibitors have almost identically in common. A PPI is selected by the anticipated therapeutic impact suggested by the distinctive pharmacokinetic features and the drug's dosing form. Antisecretory action is a characteristic that proton pump inhibitors have almost identically in common. A PPI is selected in accordance with the anticipated therapeutic impact suggested by the distinctive pharmacokinetic features and the drug's dosing form [59,71].

DISEASE

Some of the most common conditions for which PPIs are prescribed include:

Gastroesophageal reflux disease (GERD): Heartburn, chest pain, and difficulty swallowing are common symptoms of this chronic illness, which is caused by stomach acid flowing back into the oesophagus [72].

Peptic ulcer disease: This disorder causes open sores to appear on the stomach or the first small intestine segment. Abdominal pain, bloating, and nausea are a few signs and symptoms of peptic ulcers. The bacteria Helicobacter pylori, which has a spiral form and flourishes in the stomach's acidic environment, is thought to be responsible for up to 80% of ulcers. Aspirin and other NSAIDs may result in or exacerbate ulcers [73].

Zollinger-Ellison syndrome: This is a rare condition in which tumours in the pancreas or duodenum overproduce the hormone gastrin, which in turn causes excessive production of stomach acid. Just a few of the symptoms that might result from this include abdominal pain, diarrhoea, and weight loss [73].

Dyspepsia: In clinical practice, dyspepsia is a common GI disorder. Instead of being a single illness, it is a collection of symptoms that are connected to the upper GI tract, and it frequently coexists with other disease entities. Doctors should conduct a physical exam and thoroughly review the history before assuming that symptoms in patients with dyspeptic complaints are brought on by the upper GI tract [74].

It's important to note that while PPIs can be very effective for treating these conditions, they are not always the first-line treatment option. Depending on the underlying cause of the symptoms, your healthcare provider may recommend other medications, lifestyle changes, or alternative treatments before prescribing a PPI.

PPIS LONG TERM USE

Because acid promotes the digestion and ionisation of less soluble forms of dietary calcium and releases food-bound vitamin B12, prolonged use of high-dose PPIs is expected to have an impact on the absorption of calcium, magnesium, and vitamin B12.(85) PPI use that lasted longer than a year was linked to an increased risk of hip fracture, and this association was especially strong in people who had taken high-dose [75].

A BENEFIT OVER TRADITIONAL PPI FORMULATIONS:

When compared to traditional delayed-release PPIs, these extended-release formulations (ER) retain prolonged plasma concentrations and disperse drug release over a longer time, necessitating higher daily doses. The raised intragastric pH and percentage of time intragastric pH>4 for 24 hours show that the amount of medicine delivered is adequate to reach therapeutic blood levels [76].

The most recent technology available on the market, DDR, increases the mean residence duration (MRT) of dexlansoprazole compared to other ER formulations. Dexlansoprazole has a longer mean absorption time (MRT) than single-release lansoprazole, which is 5.6 to 6.4 hours compared to 2.8 to 3.2 hours. This shows that the

DDR formulation prolongs the length of drug exposure [77].

ADVERSE EFFECTS OF PROTON PUMP INHIBITORS

Although few researchers had access to them, we employed absolute measures whenever it was possible. Considering that many of the adverse effects we discuss are quite rare, Overall, there may not be many negative results [78]. (Table 2)

Table 2. Concerns regarding using proton pump inhibitors (PPIs) over a long period [79].

Types of adverse effects	Adverse effects that are especially related to PPI use
Long-term PPI-induced hypergastrinemia's effects	Increased risk of H. pylori infection Increased risk of gastric cancer Increased risk of colorectal cancer Rebound acid hypersecretion
Long-term PPI use and hypochlorhydria's infectious side effects	Increases the risk of enteric infections by C. difficile. Increased Candida infections in the mouth, oesophagus, stomach, and upper small intestine. Increased risk of small intestinal bacterial overgrowth. Increased risk of community-acquired pneumonia
Long-term PPI use-induced hypochlorhydria's non-infectious side effects	Increased rate of subsequent diagnosis of celiac disease
Long-term PPI-induced hypochlorhydria's effects on the body's ability to absorb nutrients and electrolytes	Increased risk of B12 deficiency Increased risk of bone fractures Increased risk of iron deficiency
Peculiarity Reaction to PPIs	Increase risk of chronic kidney disease
Alzheimer's disease and Dementia	Increased level of β-amyloid in the brain

PPIs often have few negative side effects. Headaches, nausea, cramps in the stomach, flatulence, diarrhoea, and constipation are the most frequent adverse effects. These adverse reactions are frequently minor, self-limiting, and independent of dosage or age. But lately, there has been more focus on the PPIs' harmful long-term effects. Numerous research has examined a range of unfavourable effects linked to prolonged PPI use [80].

Long-term use of these drugs comes with some potential risks, such as the following:

Increased risk of infections:

PPIs can lessen the stomach's acid production, which might make it simpler for some bacteria to survive and spread infection. PPI use has been linked with an increased risk of infections such as pneumonia, Clostridium difficile infection, and small intestinal bacterial overgrowth, according to research (SIBO) [81].

Another condition connected to PPI therapy is Clostridium difficile infection (CDI), a prominent cause of nosocomial diarrhoea with a high risk of morbidity and mortality.

According to a study on 136 people that looked at 19 percent of community-acquired infections and 81 percent of healthcare-acquired infections, one of the main risk factors for infection is long-term PPI use [82].

Nutrient deficiencies:

Stomach acid is necessary for the digestion of various nutrients, such as B12, magnesium, and calcium. Long-term PPI use may cause nutritional deficiencies that can lead to several health problems.

Up to 20% of elderly persons experience a vitamin B12 (cobalamin) deficiency, which has been associated with pernicious anemia, poor GI absorption syndromes, and reduced nutritional intake [83]. The majority of cobalamin insufficiency is caused by unreported and only discovered by chance, however, more severe cases

of cobalamin deficiency may show neuropsychiatric and hematologic indications that could indicate an underlying disease. The onset of achlorhydria and atrophic gastritis may affect the absorption of vitamin B12 and other crucial nutrients [84].

Kidney damage:

In several studies, long-term PPI use was linked to an increased risk of kidney damage, particularly in older adults or those with pre-existing renal disease [85–87].

Bone fractures:

Additionally, decreased stomach acid may affect calcium absorption, which is essential for healthy bones. Using PPIs for a long time has been linked to an increased risk of bone fractures, particularly in older people. Because most data come from retrospective case-control, cohort, and cross-sectional studies, there are presently no long-term prospective randomised, blinded, controlled trials to assess the potential increased risk of bone fracture associated with the use of PPIs. Osteoclasts also have proton pumps; therefore, it is speculated that PPIs may directly affect their activity, lowering calcium absorption from the bones. Even though PPIs are known to reduce the amount of hydrochloric acid produced intragastrically, which aids in calcium absorption in the small intestine [88,89].

Rebound acid hypersecretion:

When PPIs are stopped after long-term use, some people experience a rebound effect where the stomach produces more acid than usual. This can lead to symptoms such as heartburn and acid reflux, which may be worse than before starting the medication [90]. Patients who take PPIs on demand, however, do not appear to suffer rebound as a medical problem [91].

CANCER

A serious problem for human health is the widespread failures in the treatment of cancer caused by the development of drug resistance. The apoptosis of tumor cells caused by PPI is currently a significant global issue. A previous investigation found that PPIs have cytoprotective and selective apoptotic induction effects in addition to lowering stomach acid [92].

Eradication of H. pylori infection

The majority of cases of duodenal ulcers and acute and chronic gastritis are now known to be caused by H. pylori colonisation, which affects around half of the world's population [93,94]. Eradication of the condition permanently cures duodenal ulcer disease and eliminates complications and recurrences [95]. PPIs must be used twice daily for seven to fourteen days, along with two or more antibiotics, according to treatment regimens [96]. Numerous clinical investigations have shown that PPIs and antibiotics have a synergistic effect that can result in eradication rates as high as 80% to 90% [97].

Clinical Efficacy:

When used to treat GERD and disorders including erosive esophagitis, peptic ulcer disease, and Zollinger-Ellison syndrome, PPIs are quite helpful. They are also used to stop upper gastrointestinal bleeding, such as those taking nonsteroidal anti-inflammatory drugs (NSAIDs). PPIs are generally well-tolerated, with a low incidence of adverse effects.

PPIs have shown to be clinically more effective than H2RA, which have a relatively short duration of action and depending on the specific agent and whether the patient is fasting or eating, suppress acid for about four to eight hours [98]. Another drawback is that conventional H2-RA tolerance typically emerges after 2 weeks of repeated treatment, leading to a reduction in acid suppression [99].

The development of ranitidine tolerance within 5 days of continuous dosing cannot be attributed to altered drug pharmacokinetics [100].

Even PPIs taken twice daily might not be sufficient to keep intragastric acidity under control at night.

It has been claimed that taking a dose of H2-RAs before bed will help with acid control because NAB does occur in a sizable percentage of both healthy persons and GERD patients [101,102].

Safety:

PPIs are generally safe when used appropriately, but there are some concerns regarding their long-term use. Diarrhoea, headaches, and nausea are the most often reported side effects. There have been reports of a greater chance of hip fractures, infection with Clostridium difficile, and community-acquired pneumonia with long-term PPI use. However, these risks are generally low and must be weighed against the benefits of PPI therapy.

PPI use when clinically needed is strongly warranted when all the risk/benefit information is considered. Potential side effects of this class of medications are uncommon, mostly dose-related, and occasionally time-dependent. Therefore, these medications should be used at the lowest effective dose for patients with clinical diseases where their benefit has been established (such as GERD). The severity of the underlying acid-related disease and the potential for PPIs to change the course of the condition will determine the length of the treatment [103].

Despite the lack of pediatric formulations and official indications, PPIs are frequently used to treat problems linked to gastric hypersecretion in children. They are quite successful in treating GERD, hypersecretory disorders, and ulcers. With little side effects, they offer a high level of stomach acid inhibition. The main obstacle to the use of PPIs in children is the absence of comparative studies comparing the risks, costs, and benefits of anti-H2 against esophagitis reflux-related and H. pylori-negative peptic illness. The secondary restriction relates to how long-term therapy defines the safety profile [104].

Although PPIs appear to have a substantial margin of safety when used for a long time, there have been reports of potential concerns. Numerous research has looked into the potential impact of PPI therapy on vitamin B12 absorption, but no conclusive link has been found. There is a paucity of evidence that PPI medication contributes to iron insufficiency.

PPIs should be prescribed with caution to patients who are already iron deficient, and proper iron supplements should be taken into account. The use of indirect methods to measure calcium and the fact that few studies have demonstrated a link with an increased risk of fracture limit studies looking at how PPIs affect calcium absorption [105].

Clinicians should carefully assess whether PPI use is needed and suitable in geriatric patients given that these patients are at risk for polypharmacy and adverse medication reactions due to their advanced age and various chronic conditions. Additionally, if PPIs are no longer needed, doctors should think about stopping their use [106].

Pregnant women frequently complain of GERD. This is brought on by a hormonal change during pregnancy that causes a decrease in lower oesophageal sphincter tone, together with an increase in intra-abdominal pressure from the growing uterus and displaced abdominal organs [107].

CONCLUSION

In conclusion, PPIs are highly effective in the treatment of GERD and related acid-related conditions. They are generally safe and well-tolerated when used appropriately, but long-term use may be associated with some risks. The advantages of PPI medication must be compared to any possible risks, and patients should be monitored for adverse effects.

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