The Wise Long-Term Use of Proton Pump Inhibitors PPIs among Adults in Hospitals, Health Centers and Clinics

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Abstract

Background: PPIs are frequently used in hospitals, primary health care centers and private clinics. The adverse effects and interactions are numerous so, physicians' knowledge including accurate indications after confirmations of diagnosis, duration of use and follow-up are an essential part of the treatment process.

Aim: The purpose of this review tis o help health care professionals to prescribe the PPIs wisely and appropriately.

Objective: To undertake a review of the literature relating to the long-term use of PPIs

Data Sources: United States, Food and Drug Administration [FDA], PubMed, Scopus, Science Direct, Wiley, Google Scholar, major clinical guidelines, and governmental agencies.

Data Extraction: The 2 reviewers Musa Basheer Mansour and Sara Ahmedana [MBM and SEA] independently assessed the qualities of the extracted studies and summarized data of the studies for outcomes of interest and performed quality assessments based on review of published articles and the data sources.

Results: We reviewed the available evidence and summarized the long-term use of PPIs as indicated by major clinical guidelines, governmental agencies, and published studies. For instance, United States, Food and Drug Administration, American Gastroenterological Association, American Academy of Family Physicians, British National Formulary, National Institutes of Health, Randomized controlled trials, Systematic review, Meta-analysis and Observational studies.

Conclusion: This review will provide clinical practice with research evidence-based guidelines. Clinicians and physicians should follow the major clinical guidelines and governmental agencies to prescribe PPIs, follow their patients regularly to achieve the goals of treatment, to avoid adverse effects, drug interactions and reduce the costs.

Keywords: Proton Pump Inhibitors, Food and Drug Administration, Gastrointestinal Acid Disorders, Gastro-Esophageal Reflux Disorder, and peptic ulcer disease

Introduction

Proton Pump Inhibitors (PPIs) are most prescribed and used medications worldwide, since 1989 in both primary health care and in hospitals accounting for over $11 billion in expenditures annually [1,2. These drugs have enabled improved treatment of many gastrointestinal acid disorders [GIAD] and ulceration such as, Gastro-Esophageal Reflux Disorder [GERD], dyspepsia, and peptic ulcer disease [PUD] in more than 25% of the population and prevention of gastrointestinal bleeding for those who used Non-Steroid Anti-Inflammatory Drugs [NSAIDs], Aspirin or antiplatelets [3]. With an estimated 113 million PPIs prescriptions yearly, they remain one of the top-selling drug classes in United State of America [USA] [4]. The side effects and drug interactions of these drugs are reported to be enormous if used for more than 12 weeks. Therefore, the physicians should be aware about PPIs and how to use them wisely according to major guidelines and recommendations considering the patients' safety. It was observed that many patients attending hospital, private clinics, and health centers with peptic acid related health problems have been prescribed PPIs for longer duration contrary to the evidence from international best practice guidelines which suggest that these drugs should be prescribed for a definitive time depending upon the confirmed diagnoses. The PPIs have been reported to be more efficient in gastric acid suppression than the H2-receptot blockers[5]. However, evidence has shown that their long-time use has caused many side effects [6]. The first-generation PPIs (omeprazole, Pantoprazole and lansoprazole) are degraded by hepatic enzymes CYP2C19 and second-generation PPIs (esomeprazole and rabeprazole) are more stable and their plasma concentration is not strongly influenced by different CYP2C19 hepatic enzyme activities [7,8] although their plasma half-life is only 2-3 hours.

Purposes of the Review

Aim: The purpose of this review is to help health care professionals to prescribe the PPIs wisely and appropriately and, to undertake a review of the literature relating to the long-term use of PPIs

Objective: This review was designed for health care professionals to prescribe the PPIs wisely and appropriately, to follow their patients regularly to achieve the goals of treatment, to avoid adverse effects, drug interactions and reduce the costs.

Abbreviations

ACS Acute Coronary Syndrome
AIN Acute Interstitial Nephritis
CAP Community-Acquired Pneumonia
CI Confidence Interval
ECL Enterochromaffin-like
FDA Food and Drug Administration
GI Gastro-intestinal
GIT Gastro-intestinal Tract
GERD Gastroesophageal Reflux Disease
GIAD Gastrointestinal Acid Disorders
HR Hazard Ratio
HC Health Center
ICUs Intensive-care Units
N/A Not Applicable
NSAIDs Non-Steroids Anti-Inflammatory Drugs
OR Odds Ratio
PHCC Primary Health Care Corporation
PPIs Proton Pump Inhibitors
PUD Peptic Ulcer Disease
RCTs Randomized Controlled/Clinical Trials
SIBO Small Intestinal Bacterial Overgrowth
SLE Subcutaneous lupus erythematosus
SUP Stress Ulcer Prophylaxis
USA United State of America
ZES Zollinger-Ellison syndrome

Target

In the medical field: all physicians with specialty in family medicine, general practice, general medicine, gastroenterology, and general surgery.

The users of PPIs: all patients who are presenting with one of the following medical problems; GIAD, GERD, PUD, long term users of NSAIDs.

Indications and Standards

FDA release numerous safety statements and publish recommendations for PPIs use for the following areas only, either as short-term use or long-term therapy. PPIs are prescribed to the patients at appropriate dose for the right duration based on their specific diagnosis as listed below [9].

- Treatment of gastroesophageal reflux disease.
- Healing of erosive esophagitis.
- Maintenance treatment for healed erosive esophagitis.
- Treatment of gastric and duodenal ulcers.
- Treatment and prophylaxis for NSAID-induced ulcers.
- Management of pathologic hypersecretory conditions (including Zollinger-Ellison syndrome).

FDA-approved indications and doses for PPIs therapy. [1,6,9,10] [Tables 1, 2 and 3]

Table 1. FDA-Approved Indications and Doses for PPI Therapy [9]

FDA-Approved Indications	Omeprazole	Esomeprazole	Pantoprazole	Lansoprazole	Dexlansoprazole	Rabeprazole
Duodenal ulcer (treatment)	20 mg once a day	Not Applicable [N/A]	N/A	15 mg once a day for 4 weeks	N/A	20 mg once a day for 4 weeks
Duodenal ulcer (maintenance)	N/A	N/A	N/A	15 mg once a day	N/A	N/A
H pylori eradication (duodenal ulcer, reduce risk of recurrence)	Triple therapy: 20 mg bid for 10 days Dual therapy: 40 mg once a day for 14 days	Triple therapy: 40 mg once a day for 10 days	N/A	Triple therapy: 30 mg bid for 10–14 days Dual therapy: 30 mg tid for 14 days	N/A	Triple therapy: 20 mg bid for 7 days
Erosive esophagitis (treatment)	20 mg once a day for 4–8 weeks	20 mg or 40 mg once a day for 4–8 weeks, longer course may be warranted	40 mg once a day for up to 8 weeks	30 mg once a day for up to 8 weeks	60 mg once a day for up to 8 weeks	N/A
Erosive esophagitis (maintenance)	20 mg once a day	20 mg once a day	40 mg once a day	15 mg once a day	30 mg once a day	N/A
GERD (healing of erosive or ulcerative)	N/A	N/A	N/A	N/A	N/A	20 mg once a day for 4–8 weeks
GERD (maintenance of healing for erosive or ulcerative)	N/A	N/A	N/A	N/A	N/A	20 mg once a day
GERD (non-erosive symptomatic)	20 mg once a day for up to 4 weeks	20 mg once a day for longer course may be warranted	N/A	15 mg once a day for up to 8 weeks	30 mg once a day for 4 weeks	20 mg once for 4 weeks
Gastric ulcer (benign short-term treatment)	40 mg once a day for 4–8 weeks	N/A	N/A	30 mg once a day for up to 8 weeks	N/A	N/A
Gastric ulcer (NSAID-associated)	N/A	N/A	N/A	30 mg once a day for up to 8 weeks	N/A	N/A
Gastric ulcer (risk reduction of NSAID-associated)	N/A	20 mg or 40 mg once a day for up to 6 months	N/A	15 mg once a day for up to 12 weeks	N/A	N/A
Heartburn OTC treatment	20 mg once a day for 14 days, may repeat every 4 months	N/A	N/A	15 mg once a day for 14 days	N/A	N/A
Pathological hypersecretory conditions	60 mg once a day, may adjust to patient needs	N/A	40 mg bid, may increase up to 240 mg	60 mg once a day, may adjust to patient needs	N/A	60 mg once a day, may adjust

Table 2: Appropriateness of Long and Short term PPIs Therapy in 13 Clinical Scenarios of Uncertainty and Common Misuse [10]

Long term PPIs therapy appropriate > 12 weeks	Barrett's esophagus. Healing and maintenance of healed Los Angeles grade C or D erosive esophagitis. PPI-responsive esophageal eosinophilia. Idiopathic (H. pylori and NSAID/aspirin negative) peptic ulcer disease. Zollinger–Ellison disease. PPI-responsive GERD/non-erosive reflux disease. Long-term non-selective NSAID users at high-risk for upper GI complications or long-term cox-2 inhibitor users with a prior episode of GI bleeding. Anti-platelet therapy in patients at high-risk for upper GI complications (age > 65 years or concomitant use of corticosteroids or anticoagulants or history of peptic ulcer disease). Steatorrhea refractory to enzyme replacement therapy in chronic pancreatitis.
Short-term PPIs therapy appropriate (4- to 12-week course)	Healing of Los Angeles grade, A or B erosive esophagitis. Eosinophilic esophagitis. H. pylori eradication (in combination with antibiotics). Stress ulcer prophylaxis in high-risk patients (i.e., critically ill patients with respiratory failure or coagulopathy). Functional dyspepsia. Treatment and maintenance of peptic ulcer disease. Prior to endoscopy for acute upper GI bleeding. Following endoscopic treatment of a high-risk ulcer GI bleed.
PPI use not appropriate for	Corticosteroid users without concomitant NSAID therapy. To prevent bleeding from hypertensive gastropathy in cirrhotic patients. Acute pancreatitis. Stress ulcer prophylaxis in non-critically ill hospitalized patients who are not at high-risk for ulcer formation and GI bleeding
PPIs use of uncertain benefit	• PPI non-responsive GERD • Extra-digestive GERD

Table 3: Current Indications of PPIs [6]

Clinical setting	PPIs duration and dose
GERD	
1-Erosive Esophagitis (A/B)	Standard dose PPI therapy for 8-12 weeks
2-Erosive Esophagitis (C/D)	Double dose PPI therapy for 8-12 weeks
3-NERD	Standard dose PPI therapy for 4-8 weeks
4-Long-term Management (both GERD and NERD)	Standard (or half) dose PPI maintenance (continuous, intermittent or on-demand, depending on clinical characteristics of the patient)
5-Barrett's Esophagus	Long-term individually tailored PPI therapy
6- Extra-digestive GERD	Standard or double-dose PPI therapy for at least 12 weeks
Eosinophilic Esophagitis	Standard or double-dose PPI therapy for 8-12 weeks
H. pylori Eradication	Double dose, twice daily, PPI therapy for 7-14 days (in combination with antimicrobials)
Non-H. pylori-related PU disease	Standard dose PPI therapy for 4-8 weeks
Zollinger-Ellison Syndrome	High-dose (eventually twice daily) long-term PPI therapy
Stress Ulcer Prophylaxis in patients with risk factors	Standard PPI therapy by intravenous route only during ICU stay
Dyspepsia	
1.Uninvestigated Dyspepsia in Patients younger than 45 years	Standard or half-dose empiric PPI therapy for 4 weeks
2.Functional Dyspepsia (EPS phenotype)	Standard or half dose PPI therapy for 4-8 weeks
NSAID-gastropathy Prevention of gastroduodenal lesions and events	Standard or half-dose PPI therapy, starting from the very first dose of NSAID in patients at GI risk
Treatment of gastro-duodenal lesions	Standard dose PPI therapy for 8 weeks
Steroid therapy	No need for gastroprotection unless used in combination with NSAIDs
Anti-Platelet Therapy	Standard dose PPI therapy, starting from the very first dose of antiplatelet agent in patients at GI risk
Anti-Coagulant Therapy	No need for gastroprotection unless used in combination with antiplatelet therapy
PU Bleeding	Intravenous bolus of 80 mg of the available injectable PPIs, followed by 8 mg/h for 72 hours
Cirrhosis	
Hypertensive gastropathy Prevention or/and treatment of	No need for acid suppression.
esophageal ulcers after sclerotherapy or variceal band ligation	Standard dose PPI therapy for 10 days (longer treatment should be avoided taking into account the risk of spontaneous bacterial peritonitis).
Pancreatic Diseases	
Acute pancreatitis	No benefits from acid suppression
Chronic pancreatitis	Standard PPI therapy only in patients with steatorrhea, refractory to enzyme replacement therapy

The Pros of Long-Term use of PPIs

Peptic Ulcer Disease (PUD): PUD is a peptic acid injury of the stomach and duodenum [11]. This can be further categorized into a gastric or duodenal ulcer based upon the location. Helicobacter pylori and NSAIDs are main cause of PUD approximately 10-20%. Also, stress and/or dietary factors are considered [12].

GERD: long-term and maintenance of GERD and its complications. A meta-analysis that included seventeen randomized controlled trials [RCTs] including a total of 6,072 patients found that GERD treatment with PPIs was more superior than H2 inhibitor [13]. Many factors influence response to and effectiveness of treatment such as accuracy of diagnosis, access to treatment, adherence to treatment and poor compliance. One major step in optimizing PPIs treatment for GERD is educating the patient on proper timing of PPIs medication consumption as one study found that 100% of patients in the study who had refractory GERD were consuming PPI inappropriately – an hour before a meal, during a meal and at bedtime instead of the recommended 30 minutes prior to meal [14].

Prophylaxis for NSAIDs-induced Ulcers: PPIs are effective in preventing recurrence of NSAIDs-induced ulcer recurrence. Other studies also indicate that co-administration of NSAIDs and PPIs reduces the risk of gastro-intestinal tract [GIT] bleeding [15]. NSAIDs-induced gastroduodenal ulcers are estimated to account for thousands of GI complications each year, including GI bleeds, gastric pain, or even death [11]. Currently, PPIs are recommended and FDA-approved as chronic prophylaxis in individuals with high risk due to concurrent and planned long-term NSAID use, as well as acutely for the treatment and healing of active ulcers, with most cases resolving with 6 to 8 weeks of therapy [12, 16].

Barrett's Esophagus: PPIs may also have a chemo-preventive effect on Barrett's esophagus by reducing the risk of progression to esophageal adenocarcinoma. In the systemic review cited to support the assertion, none of the included studies was RCT, hence the low-level evidence. [17].

Zollinger-Ellison Syndrome [ZES] and Pathological Hypersecretory Conditions: ZES is an acid hyper-secretory condition caused by a gastrin-secreting tumor [18]. PPIs are the FDA-approved drug of choice for management and must be given chronically to control acid secretion and prevent or reduce complications and symptoms in most patients with ZES [18].

Stress Ulcer Prophylaxis: Although not FDA-approved, numerous guidelines recommend PPIs use as prophylaxis therapy in hospitalized patients. Stress ulcers may occur in patients admitted to intensive-care units (ICUs), and inappropriate management or prophylaxis treatment may lead to severe events such as GI bleeding or ulcer formation [19]. Events such as GI bleeds may occur in up to 15% of patients not on stress ulcer prophylaxis (SUP) [19,20]. Although SUP is critical to improve hospitalized patient outcomes, it should be stressed that PPIs are only approved for SUP in high-risk patients, defined as those who are critically ill and on mechanical ventilation for more than 48 hours, or those on anti-coagulation [19]. PPIs use in these patients should be limited to short-term therapy as appropriate. PPIs should not be used as prophylaxis in low-risk or non-critically ill hospitalized patients.

Other Indications: PPIs are commonly used for a variety of other indications that do not carry an FDA approval. These include as add-on therapy for patients on antiplatelet therapy with high risk of GI bleed; functional dyspepsia; and prior to or following an endoscopy associated with an acute or high risk of bleeding [21].

The Cons/Adverse Effects of PPIs

The potential AEs of PPIs classify into adverse events related to acid inhibition and adverse events unrelated to acid inhibition as represented in Table 4. Overall, the safety of PPIs remains controversial [22].

Table 4: Potential AEs [9,23]

A=Adverse events unrelated to acid inhibition	B=Adverse events related to acid inhibition
Allergic reaction to drug chemicals	Pneumonia
Collagenous colitis	Gastrointestinal infection
Acute interstitial nephritis	Gastric carcinoid tumor
Chronic kidney disease	Gastric fundic mucosal hypertrophy
Drug interaction	Changes in the gut microbiome
Dementia	Small intestinal bacterial overgrowth
Cerebral ischemic diseases	Iron deficiency
Ischemic cardiac diseases	Bone fracture
	Vitamin B12 deficiency
	Hypomagnesemia
	Gastric fundic gland polyps
	Gastric cancer
	Colon cancer
	Spontaneous bacterial peritonitis
	Hepatic encephalopathy
	Drug interaction

Adverse Events Unrelated to Acid Inhibition

- **Allergic reactions to the chemicals in PPIs:** The allergic reactions to PPIs, including anaphylaxis, pancytopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, acute liver damage, Lyell syndrome, Stevens-Johnson syndrome, interstitial nephritis, and rhabdomyolysis. Hypercreativity reactions, especially anaphylactic reactions, due to PPIs are well documented. A recent multicenter study that included chart reviews of patients with PPI-induced immediate hypersensitivity found that lansoprazole accounted for most reactions (68.3%) and PPI-induced hypersensitivity frequently manifested as anaphylaxis [24].
- **Collagenous colitis:** Collagenous colitis is complicated diarrhea characterized by diarrhea and histopathological identification of thick collagen bands beneath the colonial epithelium [25,26].
- **Increased Risk of Acute Interstitial Nephritis and Chronic Kidney Disease:** Cell- and humoral-mediated drug hypersensitivity [18]. PPIs use causes acute interstitial nephritis (ANI) and was linked to 14% of 70% of clinical cases of ANI (New Zealand). 572,661 patients without a history of ANI or other renal disease reported an increased risk of AIN with PPI use. The case-control analysis indicated that the current use of PPI increased ANI risk when compared with past use (OR=5.16 after controlling for confounding factors) [27].
- **Subcutaneous lupus Erythematosus:** Subcutaneous lupus erythematosus (SLE) has been reported in patients taking PPIs. Drug-induced SLE can occur weeks, months or even years after exposure to the drug [18].
- **Cardiovascular disease and reduced effectiveness of clopidogrel:** Some evidence suggesting that concomitant use of PPIs and clopidogrel may reduce the anti-thrombotic activity of clopidogrel and increase the risk of cardiovascular events. Clopidogrel and the Optimization of Gastrointestinal Events Trial [COGENT]: Individuals with acute coronary syndrome (ACS) who have undergone percutaneous coronary intervention are commonly prescribed antiplatelet therapy to reduce and prevent further cardiovascular complications. PPIs may be prescribed in conjunction with antiplatelet therapy to reduce risk of GI bleeding. In addition, as mentioned, PPIs are used commonly by the general populace for other acid-related disorders [28]. In 2009, the FDA issued a statement warning against the combination of the antiplatelet agent clopidogrel and PPIs due to potential drug interactions between the two [29]. Mechanistically, clopidogrel is metabolized to its active form through the same liver enzymes that metabolize PPIs,

raising concern of a potential diminished antiplatelet effect and therefore an increase in cardiovascular events [30]. Currently, data surrounding the clinical significance of this event are mixed. A 2015 meta-analysis of 31 observational studies found that individuals on PPI therapy and clopidogrel had a 30% increased risk of cardiovascular events as compared to nonusers of PPI therapy [31]. However, the four RCTs included in the review found there was no increased risk of events identified [31]. In addition, another 2015 systematic review that explored the use of PPIs and the risk of myocardial infarction found a 16% increased risk associated with use. This was found to be regardless of clopidogrel use and was not seen with H2 blocker therapy [4].

- **Potential Dementia Risk:** Increased production and degradation of amyloid and binding to tau. Decreased availability of other nutrients PPIs use increased risk of dementia in elderly persons. The evidence is supplied by two retrospective studies on a German database [18].

PPIs adverse events related to acid inhibition

- **Small Intestinal Bacterial Overgrowth (SIBO):** PPIs are a risk factor for SIBO, which is the increase in the bacterial counts in the jejunum and duodenum because of reduced gastric acid which is bactericidal. In one study, Alteration of gut microbiome, Pereira et al. (1998) reported that PPIs increased the duodenal bacterial load, but participants remained asymptomatic [32] whereas Lewis et al. (1996) reported both that PPIs caused SIBO and symptoms, including diarrhea [33]. Other studies have also reported that PPIs aggravate dysbiosis of normal flora in the small intestines, which worsens NSAIDs-related small intestinal injury [34].
- **GI Infection:** PPIs use enhanced susceptibility to infections caused by Salmonella, Campylobacter and C. difficile (OR=4.2-8.3, 3.5-11.7, and 1.2-5.0 respectively) [35]. More recent studies corroborate these findings e.g. a case-control study found an increased risk of hospital-acquired C. difficile infection in critically ill patients (OR=2.03 and CI =1.23-3.36) [36]. A recent meta-analysis of observational studies reported similar results (OR=1.81 95% CI, 1.52–2.14). Furthermore, a recent update to a cumulative meta-analysis strengthens the evidence as a significant association between PPIs use and C. difficile infection risk was demonstrated (OR= 1.26; 95% CI: 1.12-1.39). A population-based case-control study associated PPIs with an increased risk of C. difficile in infants and children [37]. In 2015, the FDA issued a public safety alert regarding increased Clostridium difficile infections associated with PPI use. This was primarily based upon a 2012 systematic review and meta-analysis study that included over 30 studies and 300,000 patients, which concluded that PPI users had a 74% higher risk of developing a C diff infection, as well as a 2.5-fold higher risk of recurrent infections, as compared with nonusers [38].
- **Respiratory Infection:** PPIs use may also lead to increased rates of pneumonia. A meta-analysis performed in 2011 showed that the risk of community-acquired pneumonia (CAP) was 34% higher in patients on PPIs, which increased with higher dosing [39]. For both C diff and CAP, it is generally hypothesized to be due to decreased gastric acidity caused by long-term PPI use and a subsequent increase in bacterial colonization [39] [40].
- **The potential risk of Gastric Neuroendocrine Tumor:** PPIs use increase the intragastric pH, plasma gastrin concentration is increased, and gastrin stimulates the proliferation of enterochromaffin-like (ECL) cells and gastric neuroendocrine tumors [41].
- **Thickening of the gastric fundic mucosa:** Increased proliferation of gastric mucosal stem cells is what causes the thickening of the gastric fundic mucosa [42].
- **Impaired absorption of micronutrients:**
  - **Magnesium** is absorbed in the small intestine and the micronutrient is important for regulation of neuromuscular activity as well as various enzymatic activities. Increased gastric pH alters Mg transport and absorption. Some cases of hypomagnesemia associated with chronic PPI use were shown in systemic review of observational studies that report a modest positive association between PPI use and hypomagnesemia (HR=1.43). In 2011, the FDA issued a warning that long-term PPI use may lower serum magnesium levels that supplementation alone may not correct unless the PPI was discontinued [43]. When severe, hypomagnesemia may present in the form of muscle weakness, tetany, seizures, cardiac arrhythmias, and hypotension, with the potential to be life-threatening [30]. The risk of hypomagnesemia was further studied by a 2015 systematic review and meta-analysis that included over 100,000 patients and assessed the risk of hypomagnesemia in patients with PPI as compared with non-PPI users. This study ultimately concluded approximately a 40% increased risk of hypomagnesemia with PPI use as compared with non-PPI therapy [44].
  - **Iron deficiency:** Evidence showed the long-term PPI use in patients with hereditary hemochromatosis result in significantly reduced iron absorption [45].
  - **Calcium:** The long use of PPIs can decrease calcium absorption because gastric acid plays an important role in the process [46]. Fractures and osteoporosis are due to reduction in calcium absorption because of increased gastric pH [47]. In May of 2010, the FDA issued a public safety statement alert regarding potential increased risk of fractures associated with PPI use [48]. Since then, numerous studies exploring the relationship between PPI use and fracture risk have been examined. A 2016 meta-analysis reviewing over 200,000 fracture cases reported a 26% higher risk of hip fracture, 58% higher risk of spine fracture, and a 33% risk of fracture at any site in individuals who used PPI as compared with those who have not, even at a duration of less than 1 year [47].
  - **Vitamin B12**, increased gastric pH alters absorption, potential for microbial overgrowth that utilizes cobalamin. There is association between PPIs and vitamin B12 absorption which depends on protein digestion **[18,46,49].**

- **Gastric Cancer:** PPIs may "play dual role" in gastric carcinogenesis and treatment of gastric cancer [50].
- **Gastrointestinal Malignancies:** High-doses of PPIs in refractory gastro-intestinal cancer because hypergastrinemia associated with PPI would stimulate the proliferation of neoplastic colonic cells and increase the risk of colon cancers [51].
- **Drug-Drug Interactions [9]:** Omeprazole have included prolonged elimination of diazepam, warfarin, and phenytoin. Isolated reports of changes in elimination have been reported with cyclosporine, disulfiram, and other benzodiazepines. No drug-drug interactions were found between esomeprazole and phenytoin, R-warfarin, quinidine, amoxicillin, oral contraceptives, and clarithromycin. Esomeprazole may interfere with the elimination of other drugs metabolized by CYP2C19. Co-administration of esomeprazole and diazepam results in a 45% reduction in diazepam clearance and increased plasma diazepam levels. Changes in gastric pH can affect the bioavailability of some medications. Examples of medications where the bioavailability of the medication may be decreased with profound and long-lasting inhibition of gastric acid secretion are ketoconazole and iron salts.

Monitoring requirements

Document the medical indication, non-pharmacological measure, duration of PPIs uses and stepping if needed. Serum magnesium checkup during the prolonged use [52]. Vit B12 and Calcium. To reduce PPIs use, stewardship program, managed by pharmacists is highly recommended to determine if use is necessary, educate patients on the proper administration, and discuss whether deprescribing is warranted. Involving patients in the decision to de-prescribe PPIs is vital for patient success. Patients who are educated on the risks associated with long-term therapy and possible side effects associated with PPIs are more likely to understand the reasoning for deprescribing and may experience better long-term outcomes [53].

Prescribing, Deprescribing & Dispensing Information

PPIs should be prescribed appropriately at the lowest effective dose for the shortest period and those who use PPIs for a long time should be checked regularly [52]. In 2017, guidelines for deprescribing PPIs were published in Canadian Family Physician. A team of healthcare professionals, including three pharmacists, collaborated to establish the evidence-based clinical practice guideline [53]. Deprescribing is reducing the dose, stopping, or using "on-demand" dosing. The guideline recommends deprescribing PPIs in adults who suffer from heartburn and who have completed a minimum treatment of 4 weeks in which symptoms are relieved. These recommendations do not apply to patients with Barrett's esophagus, severe esophagitis, or patients with a history of bleeding gastrointestinal ulcers [11]. Per the published guidelines, an algorithm can be used in determining when and how PPIs should safely be deprescribed. For patients needing occasional symptom relief, OTC antacids or H2 receptor antagonists (H2RAs) may be used on an as-needed basis. H2RAs may be used on a daily basis, although the recommendation only proves to have moderate-quality evidence. Patients should also be educated on the nonpharmacologic approaches to minimize symptoms of heartburn, dyspepsia, regurgitation, and epigastric pain. Patients should be counseled to avoid meals 2 to 3 hours before bedtime, avoid dietary triggers, and address whether weight loss is required [53].

PPIs Use after the Discharge of the Patients from the Hospital [6]

Studies in primary care and emergency offer that PPIs are extremely prescribed for inconvenient indications or offers some advantages. Hospitalized patients considerably often started PPIs inappropriately and continued, following discharge, by primary care physicians. Unsuitable recommendations for PPIs with the discharge are completely repeated and persistent. This prescription habit may lead to a continuation of PPI therapy in primary care, thereby unnecessarily increasing polypharmacy and the risk of adverse events as well as burdening the public health budget. An Italian study found that the persistence rate of PPI therapy is high, after both appropriate and inappropriate prescriptions (62 % and 71 %, respectively). The general practitioners' attitude to continuing or discontinuing PPIs depends on their level of knowledge and their perceptions of hospital physicians' competence as well as the threshold to prescribing in hospitals.

Points to be Focused on and Considered

- Confirmed diagnosis prior to prescribing PPIs and enable mandatory indication per medication.
- PPIs therapy should be evidence based.
- Practice of giving PPIs with drugs as a poly pharmacy is not a good practice.
- Physicians and clinicians must consider and know the risk of long-term PPIs use in clinical practice.
- Be aware about adverse effects, drug interactions, and adverse drug reactions reports (ADRS).
- Refill or repetition should be done on a clinical base.
- Decisions on whether to initiate or continue PPIs therapy should be sound and PPIs should only be prescribed when there is an appropriate clinical indication.
- Pharmacists should help in alerting physicians especially with long term administration and any other drug related problems (labs interpretation, discontinuation, drug interactions etc.)
- Encourage non-pharmacological approach and dietary assessment.
- Implement "deprescribing" concept including discontinuing medications, tapering the dose, reducing the dose.
- Follow up patients after deprescribing or discontinuation of therapy.

Impact in Clinical Practice

This review may guide policymakers and physicians in designing future clinical guidelines and or clinical audit programs. The findings will inform national health planning strategies by identifying the pros and cons of the use of PPIs. The physicians should follow the major clinical guidelines and governmental agencies for the best health services outcomes.

Recommendations for Research

This research will provide clinical practice with research evidence-based guidelines. In addition to that, conducting future research such as a systematic review, meta-analysis systematic, and longitudinal Cohort studies are very important in clinical practice to manage the gaps in knowledge identified from the results of this review.

Conclusion

We have presented the most current research outlining and we conclude that the use of PPIs provide benefits if prescribed appropriately. This review found a significant level of risks of long-term use of PPIs. The periodic follow-up and assessment of risks in PPIs users is very helpful. In addition to that, physicians should follow the guidelines when prescribing PPIs and must consider the advantages and disadvantages for patients.

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ANNEXES

Annex 1 ; PPIs doses: National Institutes of Health, U.S. National Library of Medicine, DailyMed Database. Provides access to the latest drug monographs submitted to the FDA. https://globalrph.com/drugs/proton-pump-inhibitors-ppis/# (54)

Esomeprazole dosing:

- Healing of erosive esophagitis: Oral: Initial: 20-40 mg once daily for 4-8 weeks. If incomplete healing, may continue for an additional 4-8 weeks. Maintenance: 20 mg once daily.
- Symptomatic gastroesophageal reflux: Oral: 20 mg once daily for 4 weeks.
- Pathological hypersecretory conditions (Zollinger-Ellison syndrome): 40 mg twice daily; adjust regimen to individual patient needs; doses up to 240 mg/day have been administered.

Lansoprazole dosing: the strength we have is only 30 mg but, if 15 mg will be added to HMC in the future.

- Duodenal ulcer: Oral: Short-term treatment: 15 mg once daily for 4 weeks. Maintenance therapy: 15 mg once daily. Gastric ulcer: Oral: Short-term treatment: 30 mg once daily for up to 8 weeks.
- Symptomatic GERD: Oral: Short-term treatment: 15 mg once daily for up to 8 weeks.
- Erosive esophagitis: Oral: Short-term treatment: 30 mg once daily for up to 8 weeks. Maintenance therapy: 15 mg once daily.
- Hypersecretory conditions: Oral: Initial: 60 mg once daily; adjust dose based upon patient response and to reduce acid secretion to <10 mEq/hour (5 mEq/hour in patients with prior gastric surgery). Doses of 90 mg twice daily have been used... administer doses >120 mg/day in divided doses

Pantoprazole dosing:

- Erosive esophagitis associated with GERD: Oral: Treatment: 40 mg once daily for up to 8 weeks. An additional 8 weeks may be used in patients who have not healed after an 8-week course. Maintenance of healing: 40 mg once daily. I.V.: 40 mg once daily for 7-10 days.
- Hypersecretory disorders (including Zollinger-Ellison): Oral: Initial: 40 mg twice daily. Adjust dose based on patient needs. Doses up to 240 mg/day have been administered.

Rabeprazole Dosing:

- Duodenal ulcer: Oral: 20 mg/day before breakfast for 4 weeks.
- GERD: Oral: 20 mg once daily for 4-8 weeks; maintenance: 20 mg once daily.
- Hypersecretory conditions: Oral: 60 mg once daily. Dose may need to be adjusted as necessary. Doses as high as 100 mg once daily and 60 mg twice daily have been used.

Annex 2; Algorithm on PPIs use (55)
PPIs Algorithm