

## Review Article

# Integrative Gastroenterology and Hepatology

## Long Term Use of Proton Pump Inhibitors: Where to Draw the Line

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### Abstract

Proton pump inhibitors are the leading evidence-based therapy for acid related upper gastrointestinal disorders including dyspepsia, GERD and peptic ulcer disease. These are among the most frequently prescribed drugs globally. However, PPIs have been subjected to studies and have been associated with increased risk of adverse effects like *Clostridium difficile*-associated diarrhea, community-acquired pneumonia, bone fracture, reduced intestinal absorption of vitamins and minerals, and more recently kidney damage and dementia etc. In this review the recent literature regarding these adverse effects and their association with long-term proton pump inhibitor treatment is discussed. The objective of this review is to analyse the potential adverse effects of long-term PPI use and summarize the clinical implications. We documented a considerable increase in the use of PPIs over the last decade. This increase is due to over-prescription and use of PPIs for inappropriate indications. On the other hand, some patients may have had PPI therapy discontinued abruptly or inappropriately due to safety concerns. However the patients with a proven indication for a PPI should continue to receive it in the lowest effective dose for a shortest possible time. Finally, in most cases and based on the available evidence, PPIs benefits seem to outweigh potential adverse effects. Large randomized prospective trials are required to more firmly establish direct cause and effect relationships between PPIs and adverse events.

### Introduction

With the discovery of Omeprazole during the late eighties, Proton Pump Inhibitors (PPIs) were first available in 1989. Since then we have a good number of available PPIs including omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole, dexlansoprazole and ilaprazole (developed in Korea and available in China) [1]. With the development of these molecules and their use in clinical practice, the management of acid related diseases and disorders have improved to a considerable extent [2]. With the advent of PPIs, elective surgical management for peptic ulcer disease (PUD) as well as anti-reflux surgery for GERD have been greatly reduced, even in developing countries and has been virtually abolished in many developed countries [2]. However, although PPIs

was considered to be relatively harmless, it has already been reported scientifically that they are associated with complications like gastric cancer, *Clostridium difficile* enteritis, bone fractures, pneumonia, dementia, acute interstitial nephritis, vitamin/mineral deficiencies etc.

The National Institute for Health and Clinical Excellence (NICE) published its guidelines on proton pump inhibitors in 2000. Its recommendations for using these drugs-particularly in the long term-are relatively selective [3]. However in most cases, PPIs' benefits seem to outweigh potential adverse effects [4]. These drugs, for efficacy and low toxicity, were approved as OTC product in 2003 and since then were probably subjected to overuse and misuse leading to long time even lifelong use beyond

recommended course of therapy without any indications [5]. During the last decade, there has been a growing concern over potential adverse effects of PPIs associated with long-term therapy and since 2010, the FDA has issued various safety warnings regarding risk of complications [6,7]. These health-related concerns are complemented by financial concerns following extensive use of PPIs [8,9].

As a consequence, the number of yearly papers reporting PPI-related adverse events and/or PPI-drug interactions as well as financial implications have steadily been increased [10]. Over the last two decades, the use of PPIs has been increased dramatically without concerns of side effects and hazards in primary care and in hospitals, both in the in-patient setting and on discharge [11-13]. In groups of patients in hospital and home facilities, overuse of PPIs has been associated with inappropriate indications and as well as associated with total lack of follow-up [14-18]. Actually it was found that long-term use of PPI occurs in 12% of the older population and for 38% of these, no disease- or drug-related reasons can be identified [19].

Unjustified and unsubstantiated use of PPIs is a matter of great concern, especially in the elderly, with comorbid conditions and taking multiple medications. Consequently they are exposed to an increased risk of long-term PPI-related complications. Inappropriate prescriptions and unjustified long-term use resulted in multiple recorded adverse effects [20,21]. Moreover, PPIs are frequently prescribed for non-dyspeptic symptoms and continued for a long time without any supervision and review [22].

More frequently PPIs are considered to be harmless and relatively inexpensive remedy for different acid related problems either real or perceived. Their use is increasing, particularly for long-term treatment, often being over-prescribed and used for inappropriate indications [23]. The prescription of PPIs without clear indications has been frequently observed in many countries in hospitals and primary care [24-26]. Actually once on a PPI, the majority of patients remain on long-term PPIs [27]. Underuse is also matter of concern despite all guidelines supporting the use of gastroprotection with PPIs in at risk patients treated with NSAIDs [28]. With a very good logic as well as adequate science, health care providers are increasingly using PPIs for prolonged periods and sometimes for lifetime. Furthermore, since PPIs are now available over-the-counter, patients can have free access to them and for a long periods of time, without seeking medical attention [29-31]. Consequently there is growing

concern for the potential adverse effects resulting from such long-term therapy [32-34].

Low-dose aspirin or NSAIDs and steroid therapy or oral anticoagulant treatment in low-risk patients, may have been frequently associated with unsubstantiated and inappropriate PPIs prescriptions [26]. Two Swedish studies found that 59-81% of hospitalized patients received acid suppression therapy without appropriate indication [24,35]. The studies for evaluation of long term use of PPIs applied different definitions of long-term use, based on either duration of therapy or used Defined Daily Doses (DDDs) per year, without taking both parameters into account [36,37].

During the last ten years there have been considerable increases in prescriptions of PPIs in US Emergency Departments which occurred despite rising safety concerns [38]. In selected groups of patients in hospital care and nursing home facilities, overuse of PPIs has been shown [39-42].

This review regarding these adverse effects and their association with long-term proton pump inhibitor therapy may be started with the indications and common use of PPIs in the contemporary use.

## **Common Use of PPIs in Contemporary Medicine (Table 1)**

### **Peptic ulcer disease**

Till date acid suppression remains the mainstay of treatment for peptic ulcer disease both for duodenal ulcer and gastric ulcer [43]. A group of studies during late nineties concluded that PPIs were significantly more effective than H<sub>2</sub>RA in achieving ulcer healing [44]. A recent meta-analysis shows that gastroprotectants, in particular PPIs, reduce the risk of peptic ulcer disease and its complications as well as promote healing of peptic ulcers. The authors recommended PPIs to be the most effective class of acid suppressor for the management of peptic ulcer disease. It confirms that gastroprotection, in particular, by means of PPIs, is associated with a roughly five times reduced risk of ulcer incidence as well as ulcer bleeding when compared with no protection [45]. One of the absolute indications for PPI use is PUD, however PPIs are not without significant adverse effects and their long-term use must be reevaluated periodically and discontinued when appropriate [46].

### **Gastroesophageal reflux disease (GERD)**

GERD includes a broad spectrum of clinical disorders

**Table 1:** Proton pump inhibitors (PPIs): Common Indications for use.

Common Indications for use of PPIs	Recommendations	References
Peptic Ulcer Disease (PUD)	One of the absolute indications for PPI use is PUD	Daniel et al 2017 [44]
Gastroesophageal Reflux Disease	For long-term medical treatment to alleviate symptoms and prevent recurrences.	Scarpignato et al 2016 [49]
H. pylori infection	Triple therapy with PPIs for 2-week treatment regimen.	Chey et al 2017 [62]
NSAIDs and Aspirin induced ulcers	PPIs reduce risk of developing gastric or duodenal ulcers in patients using NSAIDs and Aspirin .	Lanza et al 2009 [64]
Zollinger–Ellison syndrome and other hypersecretory conditions	The management of ZES needs high dose of PPIs	Thakker et al 2012 [70]
Stress ulcers & Corticosteroids Therapy	Routine stress ulcer prophylaxis is recommended with PPIs therapy for high-risk patients.	Krag et al 2014 [73]
Peptic Ulcer Hemorrhage	PPI therapy is needed in peptic ulcer haemorrhage where endoscopic facilities are not available or after endoscopic haemostasis for rebleeding.	Zhang et al 2015 [76]
Barrett's Esophagus	Role of PPIs in Barrett's esophagus is being inconclusive	Shaheen et al 2016 [79]; Fitzgerald et al 2014 [80 ]
Eosinophilic esophagitis (EoE)	PPIs therapy led to clinical response and histologic remission in patients with PPI responsive Eosinophilic Esophagitis	Abe et al 2017 [84]

from heartburn without esophagitis to severe symptoms caused by erosions, ulcers, strictures even columnar metaplasia (Barrett's oesophagus) of the lower esophagus. The disease is conditioned by retrograde flow of gastric contents through an incompetent or hypotonic LES. GERD is sub classified into esophageal and extra-esophageal syndromes in the Montreal consensus [47]. There are also a group of patients with esophageal symptoms having macroscopically normal mucosa on upper GIT endoscopy who are considered to have Non-Erosive Reflux Disease (NERD) [48].

PPIs are the mainstay of medical treatment of GERD. An Eight-week therapy with standard dose PPIs can achieve healing of esophagitis and symptom relief in more than 80 % of patients with typical symptoms, the healing rate depending on the severity of mucosal Injuries [49-51]. GERD and NERD require long-term PPI treatment on a continuous, intermittent or on-demand basis. GERD and NERD are chronic, relapsing diseases. Six months after cessation of treatment, symptomatic relapse is common and frequent (i.e., in 90 % of endoscopy positive and 75 % of endoscopy-negative patients) [52]. Maintenance therapy in GERD with proton pump inhibitors is highly

effective and certainly the best option for older patients or those at risk from surgery [53]. Surgery may be preferable to a lifetime of drug treatment for a young fit patients with frequent relapses [54].

## H. pylori infection

Gastric *Helicobacter pylori* infection causes chronic atrophic gastritis and is considered a risk factor for gastric malignancy [55,56]. Several randomized trials and a meta-analysis indicate that H pylori eradication may significantly reduce the risk of precancerous gastric lesions and anti-H pylori treatment may be an effective strategy for preventing gastric malignancy [57-59]. The rate of success of standard triple therapy is being reduced gradually and going down to 80-87% in different protocols and this is probably due to development of microbial resistance [60,61]. The 2017 American College of Gastroenterology (ACG) guidelines proposed different protocols and strategies for the treatment of *H pylori* infection all of which include PPIs [62].

## NSAIDs and aspirin induced ulcers

PPIs also are recommended to prevent non steroidal anti-inflammatory drug (NSAID)-and aspirin-induced

ulcers in high-risk patients [63,64]. Proton pump inhibitors appear to treat effectively both H. pylori-positive and H. pylori-negative ulcers, although H. pylori-negative patients are more frequently refractory to treatment. Similarly, maintenance therapy with PPIs appears to be effective in patients with either H. pylori-positive or H. pylori-negative DUs [65]. Most of the PUD actually are due to H. pylori infection and NSAID use and in combination they account for approximately 90 % of Peptic Ulcer disease [66]. Idiopathic ulcers are likely to require long term PPIs therapy, although the optimal duration of treatment is undefined and might be lifelong [67]. PPIs are also indicated for stress ulcer prophylaxis in patients with a risk of bleeding [68].

### **Zollinger-Ellison syndrome and other hypersecretory conditions**

Zollinger-Ellison syndrome is a rare disorder conditioned by formation of gastrin-producing tumor gastrinoma. The disease is characterized by sustained hypersecretion of gastric acid leading to pathogenesis of PUD with its complications such as perforation and haemorrhage. The management of ZES needs high dose of PPIs compared with those used in other acid-related disorders [69,70]. Interruption of PPI treatment in these patients leads to acid rebound and can have detrimental consequences, including complications of peptic ulcer disease [71].

### **Stress ulcers and corticosteroids therapy**

Stress-related mucosal disease i.e. stress ulcers are acute gastroduodenal mucosal lesions that can be detected endoscopically in critically ill patients. Routine stress ulcer prophylaxis is recommended with PPI therapy for high-risk patients. A number of meta-analyses found that the risk of bleeding in ICU is reduced by some 60 % in patients receiving stress ulcer prophylaxis compared with those treated with placebo or no prophylaxis [72,73].

Corticosteroids do not cause any direct injury to the gastroduodenal mucosa [74]. However, corticosteroids may increase the gastrointestinal risk of NSAID therapy and may have detrimental effects on idiopathic or iatrogenic ulcers [75]. Therefore, patients taking corticosteroid therapy having peptic ulcer disease or are under concomitant NSAID therapy, mucosal protection with a PPI is recommended [49].

### **Peptic ulcer hemorrhage**

In spite of the fact that Endoscopic manipulation is the mainstay of management of Peptic Ulcer bleeding, Int Gast Hepatol, 1(1): 20-35 (2018)

PPI therapy is needed where endoscopic facilities are not available or after endoscopic hemostasis to address re-bleeding as well as to avoid surgical interventions in high risk patients [76]. Current guidelines recommend peptic ulcer prophylaxis only for intermediate- to high-risk patients. It is suggested that no ulcer prophylaxis is necessary for oral anticoagulants, administered in the therapeutic range to patients without a history of ulcer/bleeding or concomitant NSAID treatment [77]. The PPIs may also prevent gastrointestinal complications for patients treated with cyclooxygenase (COX) inhibitors or antiplatelet agents [78].

### **Barrett's esophagus**

Role of PPIs in Barrett's esophagus is being recently debated. In a study authors advocated continuous maintenance therapy in patients with Barrett's esophagus and stressed over the potential chemoprevention of PPIs against neoplastic transformation [79]. However this is being denied by the other recommendations [80].

### **Eosinophilic esophagitis (EoE)**

Eosinophilic Esophagitis is a rare chronic immune-mediated inflammatory disorder, presented with esophageal dysfunctions like dysphagia and food impaction etc. and supported histologically by eosinophil-predominant inflammation of the esophagus [81,82]. Four therapeutic options have become available for treating patients with eosinophilic esophagitis, including dietary modifications, proton pump inhibitors, topical corticosteroids and endoscopic esophageal dilation [81]. Recent studies found that PPI therapy led to clinical response and histologic remission in patients with PPI responsive Eosinophilic Esophagitis [83,84].

### **Are PPIs all that Safe? (Table 2)**

PPIs are generally considered to be effective, safe and well tolerated, with only rare and mild side effects in short-term use. Concern and evidence on the potential long-term complications of PPI therapy are gradually emerging with time and include a good range from interaction with other drugs, increased risk of infections, reduced intestinal absorption of vitamins and minerals, and more recently kidney damage and dementia etc. [84]. A good number of contemporary comprehensive reviews have documented the majority of these events [85-87]. The adverse effects of long term PPI therapy may be grouped as complications of gastrointestinal system and extra gastrointestinal manifestations.

**Table 2:** Suggested complications of Long term PPI use with clinical significance.

Complications	Nature of evidence	Suggested Mechanism	Clinical significance
Gastrointestinal infections	Systematic review Meta analysis Case-control studies Pharmacoepidemiologic cohort study	Hypochlorohydrria enhance survival and promote germination and outgrowth of <i>C. difficile</i> spores.	Minimal; emphasizes need for valid PPI indication
Gastric Neoplasms	Case controlled study Experimental study Systemic review Meta analysis Correspondance	PPIs induced hypergastrinemia and ECL cell hyperplasia. Hypochlorohydrria -achlorohydrria-atrophic gastritis -dysplasia -anaplasia sequence	Increased number of higher quality studies are needed to confirm or refute any causal link of PPIs with gastric cancer
Vitamin/mineral deficiencies	Metaanalysis Correspondence Systemic Review Case report Population based study	Impaired intestinal absorption	More studies needed
Respiratory infection	Nested case-control study Systemic analysis Meta Analysis	Hypochlorohydrria upper GI bacterial overgrowth and potential micro-aspiration or translocation of bacteria into the lungs	Minimal; evidence is too weak
Fractures of Bones	Nested Case controlled study population-based case-control study	Hypochlorohydrria, poor calcium absorption	Either nonexistent or minor. Further studies are warranted
Neurological Manifestations	Cohort study Case control studies	Increased the levels of $\beta$ -amyloid in the brains	Randomized, prospective clinical trials are needed
Cardiovascular Complications	Retrospective cohort study Randomized, placebo-controlled, double-blind, double-dummy clinical trial	increased residual platelet aggregation and platelet activation	Prospective clinical trials and laboratory analyses of biochemical interactions are warranted
Renal Complications	Nested case-control study Systematic review population-based study	Progressive chronic interstitial nephritis due to magnesium deficiency	Low-prevalence association. Prospective randomized trials are needed

### Gastrointestinal infections

A good number of recent papers suggest that hypochlorohydrria conditioned with long term PPI therapy increases the risk of enteric infections by *C. difficile* and other pathogens. *C. difficile* infection has recently emerged as a major public health problem with increases in both incidence and mortality leading to an increase in use of antibiotics and acid suppressive drugs [88]. PPIs are postulated to increase the proliferation of spores conditioned by hypochlorohydrria [89]. As long back as 2004 use of PPIs was identified and recognized to be an important risk factor for clinical course and relapse of *C. Difficile* diarrhea [90].

There are other studies to support that long term PPI Int Gast Hepatol, 1(1): 20-35 (2018)

therapy is associated with *Clostridium difficile* infection and pseudomembranous colitis [91,92]. Recent meta analyses documented association of PPI treatment and *Clostridium difficile* enteritis [93-95]. Growing evidence suggests that acid suppression increases the risk of enteric infections by other Pathogens [96]. However in rigorously conducted systemic review and meta-analysis, very low quality evidence was established in support of an association between PPI use and risk of *Clostridium difficile* enteritis [93,97]. In any case PPIs should be used with caution in patients who are at an increased risk for *C. difficile* infection, including those immunocompromised, the elderly, hospitalized patients, and those taking broad-spectrum antibiotics [98]. Propensity for *Candida* infections in the mouth, esophagus, stomach, and upper



The hypergastrinemia secondary to prolonged acid suppression, together with a diminished calcium absorption, triggers the production of parathormone stimulating bone resorption [142]. The situations for calcium absorption with PPI use shows that the clinical effects are typically either nonexistent or minor [143]. A matched, nested case-controlled trial suggested that long term use of PPIs does not increase the risk of hip fracture in patients without associated major risk factors e.g. alcohol dependence, underlying neurological disease, accidental falls, and senility etc [144]. A study in Canada suggested that there is little or no causal association between PPI therapy and risk of fracture, and even if it is so, the risk to the patient is minimal [145].

### **Neurological manifestations**

Regular and long term use of PPIs was associated with a significant increased risk of incident dementia even after controlling for potential confounders [146,147]. However human data linking these drugs to development of dementia are conflicting [142]. The associations between statin, PPI and antihypertensive drug use, and decreased risk of dementia need further investigations [148].

### **Cardiovascular complication**

There has been significant concerns about the interaction of clopidogrel and PPIs reducing cardiovascular protection and increasing arteriosclerotic Complications [149]. There is evidence that concomitant use of PPIs might reduce the cardiovascular protection provided by aspirin [150]. Several studies have shown increased hazards of cardiovascular disease and death with PPIs [151,152]. However there are conflicting reports regarding cardiovascular complications with long term use of PPIs [153,154]. More well planned studies are needed to assess the influence of long term PPIs on cardiovascular system [155,156].

### **Renal complications**

A number of studies have shown that PPI use is associated with significant risk of acute interstitial nephritis and chronic kidney disease leading to end-stage renal disease [157-159]. A number of large population-based studies, reported a higher risk of acute interstitial nephritis and acute kidney injury in patients with long term PPI use [160,161]. In another study, it was suggested that long-term use of proton pump inhibitors is associated with increased risk of development of CKD and death [162]. PPIs are reported to be the most common cause of drug-induced acute interstitial nephritis and after PPI withdrawal and corticosteroid therapy, almost all

patients recovered a normal renal function [159,163]. Therefore, caution should be used when prescribing PPIs to older subjects especially with other risk factors for renal disease [159].

## **Discussion**

Epidemiological observations of association between long term use of PPIs and its complications like Gastric malignancies, Fractures, Renal failure, Ischemic heart disease and Pulmonary infections must be interpreted carefully to ensure proper use of PPIs according to proper indications and avoid complications in general population [164,165].

The consistency of different research findings and the growing body of evidence in the literature suggest a good number of complications associated with long term PPI use which actually may have public health concern. It is mandatory to exercise pharmacovigilance and control PPI use according to indications. Before embarking on long-term treatment, a way out to stop acid suppression must always be considered because abrupt withdrawal might be followed by rebound hyperchlorhydria and exacerbation of symptoms [36]. There are a good number of manipulation including patient education, lifestyle modification and gradual tapering of the dose which can be recommended and exercised [37].

New longer-acting compounds with extended acid suppression are being developed. They remain, no doubt, the most effective currently available medications and are widely prescribed in all age populations [166]. Vonoprazan, a member of the new generation of reversible PPIs (called potassium-competitive acid blockers), is able to achieve higher intragastric pH, effectively controlling both daytime and nighttime acid secretion [166]. Vonoprazan 20 mg b.d. inhibits acid more potently than esomeprazole 20 mg b.d. or lansoprazole 15 mg once daily [167]. Side effects of vonoprazan are insignificant [168]. Vonoprazan was also shown to exhibit an excellent healing for PPI-resistant esophagitis, indicating its potential role in treating difficult reflux esophagitis [169-171]. For the moment, vonoprazan is available only in Japan, but an international trial of comparing vonoprazan with lansoprazole in patients with erosive reflux disease in Asia, including China, Korea, Taiwan and Malaysia is underway [172]. Because of different modes of action of compared with conventional PPI and its high level antacid effect, Vonoprazan showed equivalent efficacy compared with other PPIs. Long-term administration of vonoprazan is found to be relatively free of serious side effects, and 10

mg can be recommended as a clinical dose. Vonoprazan is also effective in preventing low-dose aspirin induced gastrointestinal bleeding [173,174].

PPIs have revolutionized the management of numerous upper GI tract acid related disorders. They have been, no doubt, of enormous benefit to patients who are at risk of upper gastrointestinal ulceration and bleeding from aspirin or NSAIDs. At the same time, use of long term PPI therapy is not without risk of adverse effects. However the overall benefits of therapy and improvement in quality of life significantly outweigh potential risks. On the other hand, many recent publications have pointed out that a good number of patients are receiving PPIs unnecessarily for conditions or symptoms for which they would not have been expected to provide benefit. Thus the patients with no clinical indication for usage are only exposed to the risks of PPI adverse effects. Furthermore, many patients who are on PPI treatment for appropriate indications are receiving excessively high daily doses or for unusually long period of time. A good medical practice adheres to the policy of lowest effective dose and for the shortest possible time. Adhering to evidence-based guidelines represents the only rational approach to an effective and safe PPI therapy. Therefore, we recommend a pragmatic, "from experience" approach to this issue. Patients with a clear indication for PPI treatment should continue to receive it in the lowest effective dose. At the same time, inappropriate discontinuation of treatment with potentially serious consequences for some patients should be avoided. It is mandatory to remember that many of the current recommendations are not without conflicts. That is why it should not deter prescribers from using appropriate doses of PPIs for appropriate indications. Large randomized, prospective trials are needed to more firmly establish direct cause and effect relationships between PPIs and adverse events.

## Conclusion

Use of PPIs is increasing, particularly for long-term basis, often being over-prescribed for indications and in other way used for inappropriate indications. Furthermore, since they are now available over-the-counter, patients can have free access to them and for longer period of time, without seeking medical attention. Consequently there is growing concern for the potential adverse effects resulting from such long-term therapy. Use of PPIs should follow evidence based recommendations which has yet to be determined. Till then a good medical practice adheres to the policy of lowest effective dose and for the shortest possible time.

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