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Long Term Use of Proton Pump Inhibitors and Associated Adverse Events: A Complex and Multidimensional Clinical Issue

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Abstract

Background

Proton Pump Inhibitors (PPI), with high efficacy and low toxicity, are the most commonly prescribed and most frequently consumed medication globally. Because of their strong inhibitory effects on gastric acid secretion, they are the most potent first-line therapy for whole range of gastric acid-related disorders, notably Gastroesophageal Reflux Disease (GERD).

Methods

The objective of this narrative review is to discuss the relatedness between long term use of PPI and associated adverse events.

Results

Whereas the FDA believes that there is very little risk of serious consequences when OTC PPI are used according to the directions on the OTC label (*only intended for a 14-day course of treatment up to 3 times per year*), any deviation from the set protocol certainly poses risks. However, in some circumstances, PPI needs to be continued indefinitely.

Some recent studies, on long term use of PPI, have revealed potential adverse effects, including risks of hypomagnesemia, osteoporotic fractures, pneumonia, Clostridium difficile infection, dementia, acute and chronic kidney disease, rebound acid hyper-secretion syndrome, vitamin B12 deficiency and iron deficiency.

Conclusion

As long as PPI are prescribed appropriately for those who genuinely require them for long term, the benefits greatly outweigh the risks. However, for continuation or maintenance therapy, the fitting approach would be administering the lowest effective dose with monitoring to determine the desired effectiveness, need to dose adjustment and possibility to consider discontinuation.

Keywords: proton pump inhibitors, gastroesophageal reflux disease, inappropriate use, long term use, deprescribing

Introduction

> ***"There are three side effects of acid: enhanced long-term memory, decreased short-term memory, and I forget the third".***
>
> ***Timothy Leary (1920-1996)— American Psychologist***

The pivotal role of gastric acid in normal upper gastrointestinal functioning including digestion, absorption of micronutrients and some protective effects against bacterial infections has been well described in medical literature for centuries. However, inappropriate gastric acid secretions certainly pose pathological conditions of varying intensity. Gastroesophageal Reflux Disease (GERD) is a chronic, relapsing malady carrying a risk of significant morbidity and potential mortality from resultant complications.

Although American Gastroenterologist AsherWinkelstein, in 1934, was the first to define clinically "Reflux oesophagitis" at 85th Session of American Medical Association, it had appeared among patients earlier than that time.[1] In 1025, Persian physician Ibn Sina (980–1037) in his Magnum Opus "*Canon of Medicine*" had described dyspeptic symptoms fitting the picture of GERD.He also mentioned "Gastric headache", associated with reflux symptoms.[2]

GERD has been defined, by World Gastroenterology Organization (WGO), as "troublesome symptoms sufficient to impair an individual's quality of life, or injury or complications that result from the retrograde flow of gastric contents into the esophagus, oropharynx, and/or respiratory tract. Reflux-induced symptoms, erosive esophagitis, and long-term complications may have severely deleterious effects on daily activities, work productivity, sleep, and quality of life".[3]

The wondrous Proton Pump Inhibitors (PPI), because of their profound and consistent inhibitory effects on gastric acid secretion, remain the mainstay of treatment of GERD.[4]

The objective of this narrative review is to discuss the relatedness between long term use of PPI and associated adverse events.

Role of PPI as Potent Suppressant of Gastric Acid Secretion

> ***"I am a great believer in alkaline water which lessens the acid in my system".***
>
> ***Arnel Campaner Pineda (1967-) - Filipino Song Writer***

They are the most commonly prescribed and most frequently consumed medication globally. They selectively and irreversibly inhibit the proton pump that accomplishes the final step in acid secretion. They have been found to exert anti-inflammatory effects to prevent gastric mucosal injury by mechanisms independent of acid inhibition.[5] Moreover, they provide protection to human gastric epithelial and endothelial cells against oxidative stress.

They have been licensed by U.S. Food and Drug Administration (FDA) for treatment of GERD, PUD (gastric and duodenal ulcers), healing and maintenance treatment of erosive esophagitis, treatment and prophylaxis of NSAID-induced ulcers, treatment of Helicobacter pylori infection (in combination with antibiotics) and management of pathologically hypersecretory conditions (including Zollinger-Ellison Syndrome).[6]

Following are the PPI, currently approved byFDA, for use in various dosage forms, including enteric-coated tablets, gelatin capsules, delayed-release tablets and powdered forms for intravenous use. The first one was omeprazole (1989: Prilosec) followed by lansoprazole (1995: Prevacid), rabeprazole (1999: AcipHex) pantoprazole (2000: Protonix), esomeprazole (2001: Nexium, the S-isomer of omeprazole), and dexlansoprazole (2009: Dexilant, the R-isomer of lansoprazole).[7] Vimovo is a combination of esomeprazole and naproxen which was approved in 2010.[8]

Vonoprazan fumarate (Takecab), a novel potassium-competitive acid blocker, was approved as mono therapy for GERD, as dual therapy (Vonoprazan, Amoxicillin) and as triple therapy (Vonoprazan, Amoxicillin,Clarithromycin) for Helicobacter pylori. It was approved in Japan in December 2014 and in Russia in April 2021. The FDA approved the company's two vonoprazan-based treatments for H pylori infection, Voquezna Triple Pak (vonoprazan, amoxicillin, clarithromycin) and Voquezna Dual Pak (vonoprazan, amoxicillin) in May 2022.[9]

Over the counter (OTC) include Prilosec OTC (omeprazole), Zegerid OTC (omeprazole and sodium bicarbonate), Prevacid 24HR (lansoprazole) and Nexium 24 H (esomeprazole).[6] Hatlebakk et al ,based on a clinical trial, concluded that for better acid suppression, the PPI should be taken before a meal,[10] most preferably the first thing to be taken in the morning when taken once daily.

If twice-daily dosing is desired, the second dose should be added approximately 30 minutes before dinner. When administered orally, they are rapidly absorbed and decrease gastric acidity by 80% to 95%.[7] More rapid inhibition is achievable by intravenous formulations, of lansoprazole, pantoprazole, and esomeprazole.[11]

The Link between GERD and COPD

> ***"Increased anxiety is known to exacerbate GERD symptoms by increasing acid production.[12] Anxiety is common in COPD, and this may contribute to GERD".[13]***

The prevalence of GERD in people with COPD ranges from 17% to 78% compared to an average of 18% in controls.[13] GERD is considered to be one of the causes of chronic cough, which is a common symptom of COPD.[14] The resultant cough may increase the frequency of AECOPD.[15] The theophylline and LAMA use was significantly more common in those found to have GERD.[16] The use of bronchodilator (eg theophylline) and inhaled long-acting beta-agonists (LABA; eg salmeterol xinafoate and formoterol fumarate), anticholinergics (ipratropium bromide, tiotropium bromide) and corticosteroids may decrease the lower esophageal sphincter (LES) pressure, facilitating reflux of gastric contents.[17] The pharmacotherapy of concomitant COPD, in this way, facilitates development of GERD.

With this background, it is quite reasonable to assert that reducing gastric acid secretion may lead to a reduction in AECOPD. The PPI, because of their inhibitory effects on gastric acid secretion, are the most potent first-line therapy for those with GERD.

Additional Role of PPI as Anti-viral Therapy

> ***"It should be taken as a majoradvancement in Pulmonary Medicine that PPI, in addition to their well proven role in acid suppression, have emerged as a promising interventional tool in the prophylaxis and symptom control of AECOPD".[18]***

Chronic Obstructive Pulmonary Disease (COPD), the third leading cause of death worldwide and the fifth-ranked cause of chronic disability, is a complex, heterogeneous, dynamic, unremitting, progressive, and treatable (but not curable) systemic condition, with pulmonary and extra-pulmonary manifestations.[18] Its most common complication is an exacerbation (AECOPD), which is "catastrophic event during the clinical course of the disease" and is considered "stroke of the lungs".[19]

Whereas COPD and GERD are mutually causal, forming a viciouscircle,[20] GERD is an independent risk factor for AECOPD.[21] While PPI are first-line drugs for the treatment of GERD, their use in patients with COPD complicated by symptomatic GERD has been found to reduce the frequency of AECOPD.

A protective effect of PPI against worsening airway obstruction and reducing risk of AECOPD and mortality, in the patients with COPD complicated with symptomatic GERD, was reported in The Copenhagen City Heart Study of 9,622 patients,[22] in an American single-center retrospective analysis of 1,445 patients,[23] and in a Taiwanese study enrolling 3,485 patients.[24] In addition to their efficacy in GERD associated AECOPD, PPI have shown remarkable efficacy in those with COPD alone. A randomized single-blind controlled trial of Lansoprazole for the prevention of AECOPD, in older patients from a university hospital and three city hospitals in Japan, yielded quite promising results. The participants were randomly assigned to conventional therapies (control group) or conventional therapies plus PPI (Lansoprazole 15 mg/d; PPI group) and observed for 12 months. The number of AECOPD per person in the PPI group was significantly lower than that in the control group.[25] Although not licensed for use in COPD, the acid suppressant effects of PPI play an important role in the management of AECOPD. Of note, the efficacy is not limited to patients with COPD complicated by GERD, PPI independently and significantly, was shown to reduce risk of development of subsequent AECOPD, delaying disease progression and improving clinical outcomes.

Inappropriate Prescribing and Over-prescribing of PPI

> ***"The most common inappropriate indication for PPI treatment is prevention of gastric damage, often associated with drugs that have not proved to be harmful to the gastric mucosa".[26]***

Inappropriate PPI use is defined as "use which either occurs in the absence of a known indication, or for use for a non-absolute indication where a trial of PPI cessation

has not been considered or attempted".[27]

Although, in the available scientific literature the words "inappropriate" and "over-prescribing" are used synonymously, they are actually not. Inappropriate means "not fitting, unsuitable or untimely, prescribing medications whose risks outweigh their benefits". It could be overprescribing ("the use of more medicine than clinically necessary, in greater amounts or at more occasions than clinically necessary") or under-prescribing ("to prescribe less frequently than clinically necessary"). The other relevant terms are: misuse ("taking a prescription medication in a manner or dose other than prescribed) and off-label use (using in a manner not specified in the FDA's approved packaging label or insert).

Whereas the FDA believes that there is very little risk of serious consequences when OTC PPI are used according to the directions on the OTC label (only intended for a 14-day course of treatment up to 3 times per year), any deviation from the set protocol certainly poses risks.

Following are certain examples of injudicious use at various healthcare facilities. Overprescribing was observed in 30% of patients receiving PPIs with no clear indication, in an Italian study. Interestingly, in the same population under-prescribing was observed in 11% of patients not receiving PPI.[28]

In a cross-sectional Irish study to determine the extent and indications for PPI use in Irish acute medical wards, only 30% of those prescribed PPI were with clear indications.[29] In another prospective, multicenter observational study, evaluating all medication orders written in 37 ICUs in the United States over a 24-hour period, PPI were the most widely used off-label medication.[30] In a retrospective cross-sectional study, at two Jordanian tertiary hospitals, 52.4% of ICU patients and 87.4% of medically hospitalized patients were inappropriately receiving PPIs.[31]

A descriptive cross-sectional study conducted at the internal medicine department of a tertiary hospital in Palestine revealed that 32.5% of patients were discharged with unnecessary PPI prescriptions.[32] Similarly, in a German cross-sectional observational study, 54.5% of hospital discharge patients were given PPI prescriptions without any justification.[33] In another cross-sectional Danish study, on long term users of PPI, those with verified indications were only 27%.[34]

Whereas the "Beers Criteria for Potentially Inappropriate Medication Use in Older Adults" suggest that prolonged use of PPI is justifiable only if there is a demonstrable need for maintenance treatment (e.g., because of failure of a drug discontinuation trial),[35] overprescribing in the elderly has become an issue of serious concern.

In a Canadian study, to review appropriateness of PPI use, in elderly, non-naïve (prehospital PPI use) and "naive" (new PPI initiated in hospital) users were included. Among non-naive patients, 10% the indication for a PPI was not appropriate, and for 24% the indication was unclear. Among naïve, for 9%, the indication for a PPI was not appropriate, and for 27%patients, the indication was unclear. Amongst those discharged with advice to continue PPI, 9% were without a plan to reassess PPI indication.[36]

A study on full medication exposure in older hospitalized patients (age 84 ±7 years) in a Scottish Health Board, revealed inappropriate over prescribing in 85.8% of those prescribed PPI.[37] In a Danish study analyzing prescribing trends, it was found that those over the age of 60 years were 3.5 times more likely to be on PPI than those under 60 years.[38] However, the trends differ in different spots of the globe. In New Zealand the highest number of prescriptions for PPI were dispensed to those above 80 years, with 339 dispensed prescriptions per 1,000 registered patients compared with 242 in those aged 65 to 69 years.[39]

Indications for Long Term Use of PPI

> ***"This general consideration regarding long-term medical treatment seems especially relevant in younger individuals who may initiate PPI use that could last 70 to 80 years".[40]***

When does PPI use become long term; is an important question? In the scoping review by Haastrup et al, it was found to be ≥1 year or ≥6 months.[41] According to FDA[6] and guidelines of The UK Medicines & Healthcare Products Regulatory Agency (MHRA), it is ≥1 year.[42]

The American College of Gastroenterology continues recommending PPI as a first line treatment for GERD and in the acute phase of upper gastrointestinal and ulcer bleeding.[43] Combined with high efficacy with low toxicity, PPI are cost effective if used appropriately. In principle they are intended for short term use (for a 14-day course of treatment up to 3 times per year). However, in some circumstances, PPI needs to be continued indefinitely. The known indications include prevention of NSAID– induced ulcers, severe esophagitis, Barrett esophagus, idiopathic chronic ulcer, refractory gastroesophageal reflux disease, pathologic hypersecretory conditions (eg, Zollinger-Ellison

syndrome), and certain patients with a history of gastrointestinal ulcer with bleeding.[44]

Undoubtedly, efficacy of PPI in the prophylaxis and symptom control of AECOPD is very promising but they are not licensed for use in COPD. If a patient of COPD is put on PPI, it would certainly be for long term. The AGA's CLINICAL PRACTICE UPDATE 7 which says that "patients at high risk for upper gastrointestinal bleeding should not be considered for PPI de-prescribing",[45] would be applicable in such a situation. However, it would be imperative for the attending physician to ensure that "the dose of long-term PPI is periodically re-evaluated so that the lowest effective PPI dose can be prescribed to manage the condition".[46]

How Much Safe is Long-term Use of PPI?

"As some of the potential side effects may have an incubation time of years or even decades the risks and benefits of starting long-long PPI use should be carefully considered".26

Some recent studies, on long term use of PPI, have revealed potential adverse effects, including risks of hypomagnesemia, osteoporotic fractures, pneumonia, Clostridium difficile infection, dementia, acute and chronic kidney disease, rebound acid hyper-secretion syndrome, vitamin B12 deficiency and iron deficiency.[47] The major source of information is "FDA Adverse Event Reporting System (FAERS)" which supports the FDA's post-marketing safety surveillance program for all marketed drug and therapeutic biologic products. It contains adverse event reports FDA has received from manufacturers as required by regulation along with reports received directly from consumers and healthcare professionals. Its dates of coverage are from January 1968—present and it is updated quarterly.[48]

The issues of inappropriate prescribing and deprescribing (as and when clinically indicated) are of paramount importance and are discussed in the next paragraphs.

Hypomagnesemia

The Guidelines of both FDA[48] and MHRA[42] have warned of the risk of hypomagnesemia following prolonged use of PPI (>1 year). It was first described in 2006 in those taking PPI for more than 1 year and presenting with carpopedal and truncal spasm.[49] However, there are some reports of occurrences even after 3 months of PPI therapy.[48] Because of its involvement in numerous enzymatic reactions, magnesium is essential for life and diverse organ systems are affected by sub-optimal levels. PPI-induced hypochlorhydria decreases absorption of nutrients including magnesium .[50] The resultant hypomagnesemia is associated with impaired function of excitable membranes in nerves, muscles, and the cardiac conducting system.[51] The neuromuscular consequences include fatigue, tremors, tetany, delirium, convulsions, seizures, and carpo-pedal spasm.[52] Cardiovascular manifestations include ventricular arrhythmias, torsade de pointes, supra-ventricular tachycardia, and sensitivity to digoxin.[53]

In a cross-sectional study on inpatients at Hospital Italiano de Buenos Aires, adult patients with long-term use of PPI had a high prevalence of hypomagnesemia. Increasing age, female sex, concomitant use of drugs that impair tubular function (Cimetidine, trimethoprim, pyrimethamine and salicylates) and chronic kidney disease enhanced this phenomenon. Anemia, hyponatremia, and malignant bone disease were associated factors with PPI-related hypomagnesemia.[54]

In a meta-analysis of nine observational studies (three cohort, five cross-sectional and one case-control) with a total of 109,798 patients, the association between the use of PPI and hypomagnesemia remained significant.[55] A Bulgarian study revealed that the association with magnesium deficiency results in beta cell dysfunction, insulin resistance, reduced glucose tolerance and eventually clinically manifest type 2 diabetes.[56] Magnesium is necessary for activation of vitamin D. Low levels of magnesium and vitamin D together can lead to increased inflammation and muscle wasting.[57] Hypomagnesemia also produces impaired parathyroid hormone secretion and can lead to hypocalcemia which is generally treatable with magnesium supplements. However, according to FDA, discontinuation of PPI is required in 25% of cases.[58] The Drug Safety Update suggests measuring magnesium levels before starting PPI treatment and repeat measurements periodically during prolonged treatment, especially in those taking PPI with digoxin or diuretics.[58]

Osteoporotic fractures

The FDA has warned against the risk of loss of bone density and fracture of the spine, wrist and hip associated with high dose and long term (>1 year) use of PPI [58]; more so in post-menopausal women with a history of smoking, which is known to inhibit calcium absorption. Smoking and PPI use may have a synergistic effect on fracture risk mediated by impaired calcium absorption.[59] In a prospective French study, to assess the risk of vertebral fractures in postmenopausal women, the use of PPI was a significant and independent predictor of vertebral fracture.[60]

A placebo-controlled, double-blind, crossover trial in elderly postmenopausal women found that calcium carbonate absorption in the fasting state decreased after 1 week of omeprazole therapy.[61] A single center

randomized controlled trial in South Korea investigated the short-term effect of PPI on the biochemical parameters of bone turnover in elderly patients with gastric ulcer. It was found that administering a PPI for 8 weeks altered bone parameters, by directly altering bone metabolism via the vacuolar H(+)-ATPase in osteoclasts.[62]

In a prospective study of 55,545 women participating in the Nurses' Health Study, PPI use was independently associated with a modestly higher risk of vertebral fracture and the risk increased with longer duration of use (>12 years). Among current and former smokers, PPI use was associated with >50% increase in risk of fracture.[63] In a meta-analysis of 11 studies (5 case-control, 3 nested case-control, and 3 cohort) long term use of PPI increased the risk of any fracture and hip fracture risk.[64] In The Manitoba study, PPI use for> 5 years was associated with a significantly increased risk of osteoporosis-related hip fractures. In a case control study conducted in the University of Manitoba, it was concluded that the longer the exposure, the higher the risk, with an even higher risk in patients with ≥7 years of PPI exposure.[65]

In a UK population-based cohort study, initiation of PPI use was associated with a higher risk of knee replacement, raising concern of an unexpected risk of PPI in accelerating osteoarthritis progression.[66] A meta-analysis of 18 observational studies, involving a total of 244,109 fracture cases, revealed that PPI use was associated with a 33% increased risk for fracture at any site, a 26% higher risk of hip fracture and a 58% increase in risk of spine fracture.[67]

Although the American Gastroenterological Association (AGA) does not recommend routine BMD screening or calcium supplementation in patients receiving long-term PPI therapy, clinicians should be aware of the potential for association with fracture risk.[46]

Pneumonia

Community-acquired pneumonia (CAP) and Nosocomial pneumonia (HAP & VAP) are a significant source of morbidity and mortality in outpatient and inpatient hospital settings. The postulated mechanism is that PPI suppress gastric acid with a resultant increase in gastric pH which promotes bacterial overgrowth leading to tracheal colonization and pneumonia.

(a) Community-acquired pneumonia (CAP)

This refers to an acute infection of pulmonary parenchyma acquired outside hospital or healthcare facilities. Previous observational studies demonstrate a positive association between PPI use and the risk of pneumonia was increased by 27% with use of PPI.[69]

Another meta-analysis, based on a comprehensive literature search of articles published between January 2004 and February 2021, revealed that the incidence of CAP was higher in PPI users than non-PPI users.[70]

In a Danish population-based case-control study[71] and in a nested case-control study in the US[72] treatment with PPI, especially when recently begun, was associated with an increased risk of CAP while the risk decreased with treatment that was started a long time previously.

The medical records of adults aged ≥60 years (N = 75,050) and matching controls (N = 75,050) were analyzed to evaluate the association between the use of PPI for ≥1 year and the risk of CAP. The risk of incident pneumonia was significantly higher during the second year of PPI use compared with the first year, regardless of age or other comorbidities.[73]

Currently, there are no practice recommendations.

(b) Nosocomial pneumonia

Nosocomial pneumonia refers to an acute infection of pulmonary parenchyma acquired in hospital settings and encompasses both hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP).

- HAP refers to pneumonia acquired ≥48 hours after hospital admission.
- VAP refers to pneumonia acquired ≥48 hours after endotracheal intubation.

In a large, US hospital-based pharmacoepidemiologic cohort, acid-suppressive medication use was associated with 30% increased odds of HAP. In subset analyses, statistically significant risk was demonstrated only for PPI use.[74]

In a retrospective study of 200 patients with intracerebral hemorrhage (ICH), admitted to the First Affiliated Hospital of Chongqing Medical University, prophylactic use of a PPI, against stress-related mucosal damage, was found to be associated with a higher occurrence of nosocomial pneumonia.[75]

With the background information that VAP is the major cause of death due to nosocomial infection in ICU, with an incidence of 9% in ventilated patients [76], a randomized clinical trial was conducted in Al-Zahra University Hospital Isfahan on ventilated patients treated with acid suppressive medication. The rate of VAP was significantly higher in those treated with PPI in comparison to those on Sucralfate.[77]

Clostridium difficile Infection (CDI)

Clostridium difficile infection, a common cause of diarrhea

associated with increased morbidity and mortality, has been found to be linked to use of PPI. The relationship between gastric acid suppression and predisposition to the development of C. difficile infection (CDI) was first suggested in 1993 by Walker et al.[78] It was hypothesized to be due to survival of the C. difficile vegetative form at alkaline gastric pH.[47] Whereas the spores are acid-resistant, vegetative forms are susceptible to acidity. An elevated gastric pH may facilitate conversion from spore to vegetative forms in the upper GI tract. Risks were highest among those >80 years.[79]

The FDA[80] warns of the risk of CDI in patients receiving PPI therapy. The Guidelines for Safe Use of PPI, endorsed by the All-Wales Medicines Strategy Group (AWMSG), also recognizes this risk.[81]

In an open-label crossover trial in the US, to test whether PPI affect the gastrointestinal microbiome to facilitate CDI, it was revealed that after 4 to 8 weeks of PPI therapy, there were alterations in the gut microbiome that predispose patients to development of CDI.[82] A meta-analysis of 42 observational studies (30 case-control, 12 cohort) with 313,000 participants revealed an increased risk of both incident and recurrent CDI in patients treated with PPI.[83] Review of 8 meta-analyses and systematic reviews, including studies conducted in the US, Europe, Asia and Canada on inpatient and outpatient adults, showed a statistically significant association between PPI and CDI ranging from mild to high risk.[84]

A study, based on the UK General Practice Research Database (GPRD), revealed that those with CDI were about three times more likely to have been prescribed a PPI in the previous 3 months than people without CDI.[85] In a pharmacoepidemiologic cohort study, conducted at Beth Israel Deaconess Medical Center, secondary analysis of data collected prospectively on 101,796 discharges from a tertiary care medical center over 5-years, the risk of CDI increased with the dose of PPI.[86]

Currently, there are no practice recommendations other than the advice of FDA that PPI users who develop diarrhea that does not improve, should seek medical care.[80]

Dementia

"Dementia, as defined by WHO, is a syndrome that can be caused by a number of diseases which over time destroy nerve cells and damage the brain, typically leading to deterioration in cognitive function (i.e., the ability to process thought) beyond what might be expected from the usual consequences of biological aging. While consciousness is not affected, the impairment in cognitive function is commonly accompanied, and occasionally preceded, by changes in mood, emotional control, behavior, or motivation".[87]

The German Study on Aging, Cognition and Dementia in Primary Care Patients (AgeCoDe) included 3,327 community-dwelling persons aged ≥ 75 years and revealed that those receiving PPI had 38% increased risk of dementia.[88]

Another German prospective cohort study using observational data from 73,679 individuals aged ≥ 75 years, without dementia at baseline, also found significantly increased risk of incident dementia in PPI users.[89] In a Czechia review study, a direct association was found between the onset of dementia and depression and the long-term use of PPI.[90]

Conversely, in 2021, Bin Wu et al conducted a study to detect the association between use of six PPI and dementia events by comprehensively assessing spontaneous reports submitted to the FAERS database, an outstanding resource for pharmacovigilance analysis and post-marketing drug safety monitoring. No association between the six PPI agents and dementia events was revealed.[91]

Currently, there are no practice recommendations.

Acute and Chronic Kidney Disease

The FDA[92] has warned against PPI-associated acute and chronic kidney disease. In a US study, of those who developed CKD, 24.4% were on PPI. A prospective logistic analysis of case-control data showed higher odds for development of CKD by 10%.[93]

In a systematic review and meta-analysis to assess the association between PPI use and the risk of adverse kidney outcomes, in 2037 identified studies, four cohort and five case-control studies with ~2.6 million patients, 20.2% were PPI users. Compared with non-users, they experienced a significantly higher risk of acute kidney injury (AKI), chronic kidney disease (CKD), acute interstitial nephritis (AIN) and end-stage renal disease (ESRD).[94]

In a study, based on the FAERS database from 2004 to 2019, 3187 PPI-associated acute kidney injury (AKI) cases and 3457 PPI-associated chronic kidney disease (CKD) cases were identified. The signal strength was stronger for CKD than AKI. Moreover, PPI-related AKI was associated with a larger proportion of deaths, life-threatening hospitalizations, and disability events than PPI-related CKD.[95]

Rebound Acid Hyper-secretion Syndrome (RAHS)

Abrupt discontinuation of (usually long term) PPI is related to increased gastric acid production above pre-treatment levels.[96] However, it may occur even after courses as short as eight weeks.[97] It is advisable that patients are warned about this possibility when PPI is deprescribed.

To a significant extent, it is an avoidable problem. According to the NHS Gloucestershire Guidelines 2021, the dose of PPI should be tapered to a lower dose and an antacid and/or alginate (e.g., Peptac®) prescribed for at least two weeks. If a step-down approach does not adequately work, the PPI could be restarted at the lowest effective dose.[98]

Vitamin B12 Deficiency

The FDA warns against vitamin B12 deficiency with daily long-term (> 3 years) use of PPI. Gastric acid is required for the release of vitamin B12 from dietary proteins to facilitate absorption in the terminal ileum. This is impaired by hypochlorhydria caused by prolonged PPI use. If left unchecked, vitamin B12 deficiency can cause anemia or neurologic damage.

A case-control study, within the Kaiser Permanente Northern California population, assessed the association of B12 deficiency with acid suppression therapy including PPI. Those who had received PPI treatment for more than 2 years had a 65% increased risk for vitamin B12 deficiency when compared with nonusers. The risk was dose-dependent.[99] Given that physiological stores of vitamin B12 in the general population are generally sufficient, current guidelines do not recommend monitoring vitamin B12 levels in patients receiving long-term PPI treatment.

However, the elderly and malnourished may be at a higher risk, as they are more likely to have borderline baseline levels.[100] The MHRA, in June 2022, recommended monitoring patients on Metformin for reduced B12 levels. This is likely to be of particular importance if they are on concomitant PPI.[101]

Iron Deficiency

Since gastric acid converts dietary iron from its ferric to its ferrous form, PPI induced hypochlorhydria can potentially lead to malabsorption of iron. Left untreated, the resultant iron deficiency can lead to anemia, asthenia, and other complications. In a U.S. community-based case-control study, ≥2 years' use of PPI was associated with an increased risk of iron deficiency. The association was stronger with higher daily dose.[102]

Protocol for Deprescribing PPI

> ***"Asking patients about all medication use, including over-the-counter drugs, and understanding why a patient is using a PPI are imperative to identifying deprescribing needs and reducing adverse drug effects".[103]***

Deprescribing has been defined as the "systematic process of identifying and discontinuing drugs when existing or potential harms outweigh existing or potential benefits within the context of an individual patient's care goals, functional status, life expectancy, values, and preferences".[104]

It needs to be emphasized that there are certain clinical conditions for which deprescribing should NOT be attempted. They include:[45]

- "Patients with complicated gastroesophageal reflux disease, such as those with a history of severe erosive esophagitis, esophageal ulcer, or peptic stricture, should generally not be considered for PPI discontinuation".
- "Patients with known Barrett's esophagus, eosinophilic esophagitis, or idiopathic pulmonary fibrosis should generally not be considered for a trial of de-prescribing".
- "Patients at high risk for upper gastrointestinal bleeding should not be considered for PPI de-prescribing".

The relevant clinical questions regarding deprescribing PPI are: should it be just on speculative risks or have a set protocol? Should it be abrupt or gradual?

In principle, the exact approach to put some patient on PPI should be with true indication, appropriate dosing schedule and periodic evaluation (need for continuation, nature and extent of PPI-associated adverse events (PAAEs), adjustment of dosage, plan to deprescribe as and when indicated). These issues have been meticulously discussed in the Best Practice Advice of American Gastroenterological Association (AGA) - 2022.[45] The key points are as following:

- "All patients taking a PPI should have a regular review of the ongoing indications for use and documentation of that indication".

- "All patients without a definitive indication for chronic PPI should be considered for trial of de-prescribing".
- "PPI users should be assessed for upper gastrointestinal bleeding risk using an evidence-based strategy before de-prescribing".

A Japanese randomized controlled trial, looking for strategies for the discontinuation of PPI, in patients on long-term treatment, is in progress with a proposed end date of August 2023.[105]

The best practical approach, at present, is to attempt reducing dose to a minimal effective level. The All-Wales Medicines Strategy Group argues that long-term PPI prescriptions should be reviewed at least annually.[81] Such an approach will not only reduce prescribing costs but will potentially increase patient safety.

The AGA Clinical Practice Update[45] argues that, in view of the PAAEs, "de-prescribing is an important strategy to lower pill burden while reducing real costs and theoretical risks". However, "the decision to discontinue should be based solely on the lack of an indication for PPI use, and not because of concern for PAAEs".

Where deprescribing of the PPI is deemed appropriate, a "step-down approach" is advisable, for example to reduce the dose every second day, and then to stop. STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions) criteria are evidence-based used to review medication regimens in elderly people.[106]

In an American study, conducted in a family medicine setting on eligible patients taking a long-term PPI for GERD without a clear indication, a unique pharmacist-managed PPI tapering schedule was developed and implemented to deprescribe PPI therapy. It was found that 86% of them were able to successfully discontinue PPI and an additional 9% reduced their PPI dose or frequency of use.[107]

Discussion

"Prescribers are responsible for determining whether PPI use is absolutely or conditionally indicated and, when uncertainty exists, to incorporate patient perspectives into PPI decision making".[45]

The systematic review by Shanika et al, the first to describe global PPI use patterns by demographics and medication factors, provide evidence on actual PPI use in the general population. The available information should be used to develop and update PPI prescribing policies to improve the safety of PPI use.[108]

Undoubtedly, PPI combined with high efficacy and low toxicity, are safe and cost-effective, if used appropriately. However, their off-label long term use is prevalent, with up to 65% of users in the United States,[44] without documented ongoing indications.

In view of the seriousness of the issue, Daniel Marks argues that it is the time to limit the inappropriate prescribing of PPI, and support deprescribing in patients on long-term therapy in whom the original indications no longer apply.[109] For those with a documented indication for long term use, it is the responsibility of prescribers to ensure that the expected benefits are balanced against the risks of PPI therapy. How to achieve this goal? Why not to revert to The Drug Utilization Review (DUR)?It involves a comprehensive review of a patient's medication and health history before, during, and after dispensing in order to attempt to achieve appropriate therapeutic decision-making and positive patient outcomes. It has been defined by American Society of Health System Pharmacists (ASHP) as "an authorized, structured, ongoing review of prescribing, dispensing and use of medication".[110] Its purpose is to ensure use of the drugs appropriately, safely and effectively to improve patient health status and to reach this goal it is classified in three categories:

- Prospective - evaluation of a patient's drug therapy before medication is dispensed.
- Concurrent - ongoing monitoring of drug therapy during the course of treatment.
- Retrospective - review of drug therapy after the patient has received the medication.

The entire process, if carried out methodically, would solve many clinical issues relating to the criteria of prescribing and that of deprescribing.

Conclusion

"Any doctor will admit that any drug can have side effects, and that writing a prescription involves weighing the potential benefits against the risks".

Mark Udall (1950-) -- US Politician

As long as PPI are prescribed appropriately for those who genuinely require them for long term, the benefits greatly outweigh the risks. However, for continuation or maintenance therapy, the fitting approach would be administering the lowest effective dose with monitoring to determine the desired effectiveness, need to dose adjustment and possibility to consider discontinuation.

Of note, PPI do not show tolerance phenomenon, even after long-term use.[111]

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Conflicts of Interest

The author declares that he has no direct and indirect financial, commercial, personal/career affiliation with the article, counting any individually held viewpoint that are relevant to this work, to disclose.

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