Key Considerations From a Health Authority Perspective When Proton Pump Inhibitors Are Used to Treat Gastroesophageal Reflux Disease (GERD) and Their Implications

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Abstract

The growing prevalence of gastroesophageal reflux disease (GERD) needs to be carefully managed to relieve the symptoms and prevent complications. Complications of GERD can include erosive esophagitis, Barrett’s esophagus and gastrointestinal (GI) bleeding. Proton pump inhibitors (PPIs) are typically first-line treatment for GERD alongside lifestyle changes in view of their effectiveness and cost-effectiveness. However, there are concerns with adherence to dosing regimens and recommended lifestyle changes reducing their effectiveness. There are also concerns about potential complications from chronic high-dose PPIs. These include an increased risk of chronic kidney disease, cardiovascular events and infections. Recommendations to physicians include prescribing or dispensing the lowest dose of PPI for the shortest time, with ongoing patient monitoring. Activities among community pharmacists and others have resulted in increased dispensing of PPIs without a prescription, which can be a challenge. PPIs are among the most prescribed and dispensed medicines in view of their effectiveness in managing GERD. However, there are concerns with the doses prescribed and dispensed as well as adherence to lifestyle advice. These issues and challenges need to be addressed by health authorities to maximize the role and value of PPIs.

Categories: Gastroenterology, Public Health, Therapeutics
Keywords: hydrogen-potassium adenosine triphosphatase enzyme system antagonist, gastric reflux, thereinafter, connotation, acid reflux, gastroesophageal reflux disease (gerd), therapeutic intervention, proton-pump inhibitors (ppi), public health force viewpoint, principal scrutiny

Introduction And Background

Gastroesophageal reflux disease (GERD) is a digestive disorder resulting from the effortless movement of gastric contents into the esophagus or beyond, which results in troublesome symptoms or more serious complications [1-3]. These include heartburn, a burning sensation in the chest, acid regurgitation, or an ongoing cough [1,3]. Serious complications include dysphagia and Barrett’s esophagus, potentially leading to esophageal adenocarcinoma [3]. GERD is a common condition, often due to abnormalities in the lower esophageal sphincter [4,5], with a pooled global prevalence of 13.3% or more of the population reporting at least weekly symptoms with rates increasing; however, with appreciable geographical variation [1,3,6-10]. Weekly prevalence rates currently range from 2.5% of the population in China up to 51.2% in Greece [6]. Typically, the highest rates are seen among South Asia and Southeast Europe countries at more than 25% of the population, with the lowest rates observed in Canada, France, and Southeast Asia at a prevalence of less than 10% of the population [6]. High prevalence rates are also seen in Nigeria, with prevalence rates increasing [1,11-14]. As a result, GERD is typically the most frequent gastrointestinal disorder across countries [3], with consultation rates in ambulatory care ranging from 5.4% to 56% of all consultations [15,16]. GERD, though cannot be classified as a single disease, is often used as an umbrella term [1,17].

Several lifestyle factors are associated with GERD, including limited exercise, high-fat diets, and alcohol [3,8,15,18,19]. The cornerstone for managing patients with GERD remains lifestyle changes, emphasizing the need to address these factors [1,20-22]. Potential lifestyle modifications include raising the head of the bed,
physical exercise including post-dinner walks, reducing smoking and alcohol intake, weight loss in obese patients, avoidance of significant food intake at least two hours before bedtime, especially in patients with nocturnal symptoms, having smaller meals more frequently as opposed to large meals, particularly in the evening, as well as introducing protein-rich meals and a vegetarian diet \[8,18,20,23,24\]. However, a concern is that lifestyle changes can be overlooked with the increased availability of low-cost treatments, notably in community pharmacies, drug stores, OTC vending machines, and supermarkets, coupled with variable knowledge of GERD among community pharmacists \[25-28\].

**Key points**

I. GERD is a common condition across countries, with prevalence rates continuing to grow.

II. Optimal management includes lifestyle advice and medical management, which is increasingly PPIs. The combined approach can help enhance the quality of life of patients as well as reduce potential complications of erosive esophagitis and Barrett’s esophagus.

III. There are concerns with chronic PPI use, especially with high doses, as this can lead to complications unless addressed with key concerns, including potentially enhancing polypharmacy and chronic kidney diseases, fractures, and infections as well as potentially enhancing polypharmacy. However, this must be balanced against their undoubted effectiveness.

IV. Potential concerns can be addressed by only prescribing or dispensing PPIs for relevant indications, providing advice on the optimal timing for administration, and regularly monitoring patients. Alongside this, encouraging adherence to lifestyle advice.

V. Community pharmacists and others are well-placed to monitor patients and offer advice. Consequently, there can be concerns with OTC vending machines containing PPIs unless addressed; however, this may be less of an issue with doses of PPIs available as OTC pharmaceutical products.

**Review**

**Medical management of GERD, including activities of health authorities**

GERD needs to be actively managed to prevent complications, which can arise from the disease itself, in addition to heartburn and associated pain, subsequently affecting patients’ quality of life \[12,29\]. Dominant complications of GERD include dysphagia, with an appreciable number of patients with dysphagia having acid-related disorders \[3,30\] and bleeding from erosive esophagitis. The prevalence of erosive esophagitis ranges from 6.4% in China up to 15.5% in Sweden in patients with symptoms of GERD \[3,31,32\]. Approximately one-quarter of non-erosive reflux disease (NERD) patients have erosive esophagitis on repeat endoscopy two years later \[3\]. This is a concern since between 2003 and 2006, in the USA, there were approximately 10,570 hospital admissions annually due to erosive esophagitis \[3,33\]. Barrett’s esophagus is also a complication with GERD following on from NERD and dysphagia, with some studies suggesting erosive esophagitis as a major risk factor for Barrett’s esophagus, with up to a fivefold increased risk \[9,34,35\]. The risk of Barrett’s esophagus increases with the length of time of untreated GERD \[36\] and is typically a precursor to esophageal adenocarcinoma \[3,35,37\]. Eusebi et al. recently estimated the pooled prevalence of patients with confirmed Barrett’s esophagus in those with GERD at 7.0%, higher among those who drank alcohol \[17\].

Antacids, alginates, histamine (H\(_2\)) receptor blockers, or proton pump inhibitors (PPIs) are typically a first-line medical treatment for patients with GERD \[1,38-40\]. In recent years, PPIs, e.g., omeprazole, which work by covalently binding to the proton pumps that control the final step of gastric acid production, thereby decreasing it, have become the treatment of choice for patients with GERD, with a number of studies showing superiority over H\(_2\) receptor blockers \[5,38,41-49\]. Typically, a standard dose of a PPI provides complete relief in approximately 70 to 80% of patients with GERD within a week \[1,50-53\], with limited differences in effectiveness between twice-daily and once-daily PPIs \[54\]. However, some studies have suggested otherwise \[55\].

A double dose of PPIs can also potentially be administered in patients with GERD not responding to a single dose \[1,47,56,57\]. The long-term use of double-dose PPIs has been found to be safe; however, their prolonged use should be limited to situations where the benefits outweigh the risks \[5,58-60\]. In addition, patients are regularly reviewed \[5,60\]. Alternatively, prokinetics can be added to PPIs to improve their effectiveness (Figure 1) \[61\].
Despite their undoubted effectiveness, compliance with PPIs is important for the optimal management of patients with GERD [20]. This should be combined with compliance with counseling on lifestyle changes [62], with weight loss potentially reducing PPI doses [22]. Overall, optimal dosing of PPIs combined with lifestyle management appears to be the most effective and cost-effective approach to managing patients with GERD where lifestyle changes are insufficient [1,5,20,44].

Compliance with PPIs can, however, be of particular concern if patients obtain these medicines over the counter (OTC) or via OTC vending machines without support and advice from healthcare professionals (HCPs), including community pharmacists [20,63]. This is because studies have shown that if patients are not fully compliant with taking their PPIs, i.e., not consuming certain PPIs, i.e., not consuming medication 30 minutes prior to a meal, they can become refractory and cause adverse impacts to patients [64]. Overall, 40% to 50% of patients do not comply with optimal timing, and poor compliance is an important reason for PPI failure [44,57]. Concerns are enhanced by the fact that compliance with PPI dosing regimens generally decreases over time, although compliance rates are higher in patients with Barrett’s esophagus [65]. PPIs taken before supper appear to be the most effective [66], with the potential monitoring of stomach pH levels to detect non-responders [67]. Although monitoring the stomach pH levels is considered the model diagnostic procedure to obtain outstanding clinical outcomes among PPI recipients. However, surveillance of pH in ambulatory care is often inconvenient, cumbersome, and expensive, impacting routine use [4, 68,69].

More countries are making PPIs available OTC, which will continue [70]. Community pharmacists can play a key role in identifying patients with appropriate symptoms of GERD as well as improving medication compliance, with the use of OTC PPIs increasing due to the convenience of community pharmacies, negating the need for patients to consult a physician with their symptoms with potentially increased costs [15,53,71,72]. In identifying patients with GERD, community pharmacists must be skilled in good history-taking regarding the patient’s symptoms, medication use, lifestyle, and communication. This will ensure that they ask the correct questions to be able to make an informed decision and recommend the correct
product [25]. Community pharmacists can also suggest referrals to a physician where there are concerns, which include multiple episodes of GERD per week, persistent or recurrent symptoms after a month of taking OTC PPIs, or unintentional weight loss [53,73,74]. This builds on multiple studies demonstrating improvements in patient care following input from community pharmacists across disease areas [75-77].

With PPIs firmly established as a first-line pharmacologic treatment for patients with GERD [1,5,20,44,47], which PPI to prescribe should be based on key issues, including their effectiveness, safety, and cost-effectiveness as these can be appreciable cost variations between the different PPIs [55]. In their review, Graham and Tansel (2018) and others have concluded that all PPIs are functionally equivalent [55,78]. This echoed the beliefs among health authorities across Western Europe when generic omeprazole first became available at appreciably lower prices than patented PPIs [79-82]. Multiple demand-side measures introduced by several health authorities, alongside measures to appreciably lower the prices of multiple-sourced PPIs, resulted in low overall expenditure on PPIs in the Netherlands, Sweden, and the UK, despite appreciably increased utilization [81-86]. In Scotland, combined supply- and demand-side measures decreased PPI expenditure by 67% between 2001 and 2016 despite a three-fold increase in utilization with generic PPIs priced as low as 8.5% of pre-patent loss prices [83]. A similar picture was seen in Sweden with expenditure on PPIs, adjusted for population size, one-tenth of that seen in Ireland in 2007 with its limited demand-side measures encouraging the preferential prescribing of low-cost multiple-sourced PPIs [81,84]. Three-monthly contracting in the Netherlands resulted in prices of generic omeprazole being as low as 2% of pre-patent loss prices, which resulted in considerable savings [82].

Low prices for PPIs are important in countries given appreciably increased utilization over the last 10 to 20 years, especially countries with universal healthcare and competing demands on available resources, with published studies showing no difference in the effectiveness and safety of generic versus originator PPIs, like other disease areas [87-92]. Low-cost multiple-sourced PPIs are also essential for patients with GERD in low- and middle-income countries (LMICs) with their high patient co-payment levels. When family members become ill, this can have catastrophic consequences for the rest of the family [92-93]. The availability of low-cost generic PPIs in several Central and Eastern European countries has also enhanced their use following the easing of prescribing restrictions [96,97]. However, there have been concerns with the quality of generics in some LMICs, which need to be addressed, to enhance the use of multiple-sourced PPIs in patients with GERD [84,98]. According to the WHO, as many as one in 10 medicines sold in low- and middle-income countries are either substandard or falsified. Initiatives such as the Lomé initiative for counterfeit medicines can help here alongside health authorities and community pharmacies regularly checking the packaging and content of PPIs supplied, including OTC PPIs [99], building on similar initiatives with herbal medicines [100]. There can, though, be concerns with the level of checking among community pharmacists in some LMICs [101,102].

Despite their undoubted effectiveness, up to 50% of patients with GERD have persistent symptoms, and up to 44% have partial or no response to PPIs [51]. This is a concern as a poor response will have an impact on the patient’s physical and mental health [51]. Treatment options at this stage include vonoprazan, a potassium-competitive acid blocker, either alone or with PPIs [1,103,104]. However, longer-term studies are needed to fully evaluate its place in treatment, especially with the availability of low-cost multiple-sourced PPIs [1]. Anti-reflux surgery is another option in pertinent patients [1,20,105,106]. PPIs may, though, still be needed after surgery to improve patient-relevant outcomes [20,107]. Endoluminal therapies are also increasingly being used for managing patients with refractory GERD (Figure 2) [20,47,108]. These approaches, though, are outside the scope of this paper.
In addition to these issues, there are concerns with the long-term complications of PPI use and the potential impact on enhancing polypharmacy and associated matters. However, these concerns must be balanced against their undoubted effectiveness especially given issues with the complications of GERD as well as patients still being admitted to hospitals with stomach ulcers [5,83]. In addition, these issues and concerns may be less of a problem at doses of PPIs available OTC [74].

### Potential overuse of PPIs and the implications

The practice of self-medication is common worldwide, including in LMICs and high-income countries, and may even be more common than prescribed medicines, especially in LMICs [109,110]. OTC medicines provide symptomatic relief and a solution to individuals having immediate health problems, as well as lower costs for patients where there are high co-payments for physician visits and travel costs, which can be catastrophic for some families [15,72,95,111]. However, the inappropriate use of OTC medicines can have potential dangers, including incorrect self-diagnosis, adverse events and hazardous drug-drug interactions, incorrect choice of therapy and dosing, and masking severe disease [109,112-114].

The high prevalence of GERD, the effectiveness of PPIs versus antacids and H₂ receptor blockers, coupled with their low prices with multiple sources now available, has resulted in PPIs becoming one of the most utilized medicines across countries, especially among high-income countries [115-117]. Other factors increasing PPI use include their increased prescribing as prophylaxis for elderly patients with arthritis as well as those on multiple medications. In addition, patients are being prescribed PPIs alongside anti-coagulant therapy to reduce potential GI bleeding and avoidable hospital admissions [83,118-121]. However, these combined factors have resulted in the potential overuse of PPIs leading to possible complications [83,117,118]. Mares-Garcia et al. found that over a third of patients over the age of 60 years had no obvious reason for being prescribed a PPI [116], which needs to be addressed.

The overuse of PPIs can increase polypharmacy, especially in the elderly, with challenges of adherence to prescribed medicines alongside increasing adverse drug reactions (ADRs) [122,123], which is a concern for health authorities. ADRs can be problematic as they increase morbidity, mortality, and costs [124-126]. There is also an increased risk of chronic kidney disease and fragility fractures in patients taking PPIs long-term, resulting in advice from HCPs and health authorities for patients to increase their calcium and Vitamin D intake, especially among the elderly [83,127-130]. However, other studies have failed to show an association between long-term PPI use and changes in bone mineral density [59,151].
Increased counseling by community pharmacists, helped by training, alongside increased patient education, can help address polypharmacy issues as well as adherence concerns when combined with general discussions on the patient’s symptoms to direct appropriate care [25,55,132]. Patients on chronic PPIs should also ideally have their serum magnesium levels regularly checked if they are also taking medicines known to cause hypomagnesemia [130,135]. Again, this can be difficult for patients to obtain their PPIs from pharmacies and other outlets, including OTC vending machines, as well as among ambulatory care physicians, unless there are recall systems in place to regularly undertake medication reviews. This, though, may again be less of an issue when patients are using PPIs for a short duration.

There may also be an increased risk of cardiovascular and cerebrovascular events linked with chronic PPI treatment, especially among patients prescribed anti-platelet medicines; however, there is conflicting evidence [134-138]. Prescribers may want to keep this in mind when managing patients with GERD and cardiovascular diseases, and pharmacists and their assistants when dispensing PPIs. Alongside this, there can be an increased risk of small intestinal bacterial overgrowth as well as enteric infections with chronic PPIs [139-143]. This was a concern during the recent COVID-19 pandemic, with studies suggesting a dose-response relationship between PPIs and COVID-19, with patients taking lower-dose PPIs appearing at reduced risk of COVID-19 [159]. However, there have been concerns that these findings were based on cross-sectional studies [139]. In any event, this may now be less of an issue with the availability of effective vaccines against COVID-19 [144,145].

Concerns with the potential adverse effects of chronic PPI use have resulted in guidance from health authorities across countries, including Scotland, to prescribe the lowest possible dose and regularly review patients on long-term PPIs [16,83,145,146]. Alongside this, regularly monitor prescribed doses of PPIs [16,83,147]. This builds on general advice in Scotland over several years to reduce the doses of PPIs prescribed for patients on chronic medication as well as monitor general prescribing [83,146]. However, these concerns and issues with the current overuse of PPIs, especially in high-income countries, need to be balanced against the undoubted effectiveness of PPIs in preventing and healing ulcers, controlling symptoms of GERD, and limiting the progress of patients toward erosive esophagitis and potentially Barrett’s esophagus with its associated implications. In addition, reducing hospital admissions arising from GI bleeds.

Next steps for better clinical outcome

PPIs should be prescribed for GERD only when clinically indicated, in a brief course, and in the smallest possible dose. PPIs receiver should be regularly monitored, especially those at increased risk of complications and taking multiple medications [117,139]. In addition, health authorities must keep an eye on physician compliance with agreed guidelines, with subsequent compliance to guidelines improving future care [115,148-150]. Additionally, there are reports that PPIs are often obtained or procured from OTC vending machines and non-pharmacy stores without appropriate medical prescribing advice. These apprehensions are possible to minimize with the low doses of PPIs available in OTC and OTC vending machines helping with testing and social distancing during pandemics [27,151]. Heath authorities must keep track of pharmacy shops to stop selling PPIs without a prescription, including self-medications.

Conclusions

There is a growing use of PPIs across countries to manage patients with GERD. However, there are concerns with their chronic use as well as with compliance and adherence rates in practice. This has resulted in advice from health authorities and others to prescribe PPIs Together with this, HCPs need to enhance patient compliance to PPIs and their dosage regimen, as well as other prescribed medicines, alongside agreed changes in their lifestyle, to help alleviate their symptoms and reduce future complications.

Community pharmacists are well-positioned to ensure that PPIs are used appropriately and effectively while also working with patients to reduce their overuse of PPIs. Pharmacists can provide effective counseling to help ensure PPI use is for agreed indications with the lowest effective dose dispensed for the shortest time. Complementary to this, conveying the importance of adherence to lifestyle changes as well as suggested dosing regimens for PPIs to improve symptom control and optimize the likelihood of treatment success. Consequently, PPIs should only be available as prescribed and health authorities should implement stringent policy monitoring. We will be following this up in future research. These suggestions and activities also working with patients to reduce their overuse of PPIs. Pharmacists can provide effective counseling to help ensure PPI use is for agreed indications with the lowest effective dose dispensed for the shortest time. Complementary to this, conveying the importance of adherence to lifestyle changes as well as suggested dosing regimens for PPIs to improve symptom control and optimize the likelihood of treatment success. Consequently, PPIs should only be available as prescribed and health authorities should implement stringent policy monitoring. We will be following this up in future research. These suggestions and activities will continually be monitored by health authorities, especially with increasing rates of GERD with rising obesity and elderly rates across countries.

Additional Information

Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no
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