

Pneumologia

Proton Pump Inhibitors: Promising Role in the Prophylaxis and Symptom Control of Acute Exacerbations of Chronic Obstructive Pulmonary Disease

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Abstract

English:

Chronic Obstructive Pulmonary Disease (COPD), the third leading cause of death worldwide and the fifth-ranked cause of chronic disability is usually associated with significant concomitant chronic diseases, Gastroesophageal Reflux Disease (GERD) being the commonest. Exacerbations of COPD (AECOPD) are episodes of worsening of symptoms, the frequency of which increases with the severity of COPD. AECOPD is triggered mainly by respiratory infections, bacterial or viral or both. Human rhinoviruses (HRV) are the top viral pathogen in triggering AECOPD, and experimental infection has provided significant new evidence in establishing a causal relationship between virus infections and AECOPD.

Proton pump inhibitors (PPI), the most potent acid suppressants, are commonly prescribed for isolated GERD or GERD complicating COPD. There has been a breakthrough in Pulmonary Medicine in that PPI, in addition to their well proven role in acid suppression, has emerged as a promising interventional tool in the prophylaxis and symptom control of AECOPD. This efficacy is not limited to patients with COPD complicated by GERD, since PPI also independently and significantly reduced the risk of developing frequent AECOPD in those with COPD alone, delaying disease progression and improving clinical outcomes. Although the studies conducted so far regarding effectiveness of PPI had promising results, current evidence is insufficient to determine to what extent their long-term use is safe. Large scale multi-center studies are warranted to assess their long-term safety profile and clinical outcomes.

The objective of this study is to identify a possible role of PPI in prophylaxis and symptom control of AECOPD.

Keywords

COPD • AECOPD • GERD • PPI • HRV

Inhibitorii pompei de protoni: rol promițător în profilaxia și controlul simptomelor acute ale exacerbarii bolii pulmonare obstructive cronice

Rezumat

Romanian:

Boala pulmonară obstructivă cronică (BPOC), a treia cauză principală de deces la nivel mondial și a cincea cauză de dizabilitate cronică, este de obicei asociată cu boli cronice concomitente semnificative, boala de reflux gastroesofagian (BRGE) fiind cea mai frecventă. Exacerbările BPOC (AECOPD) sunt episoade de agravare a simptomelor, a căror frecvență crește odată cu severitatea BPOC. AECOPD este declanșată în principal de infecții respiratorii, bacteriene sau virale sau ambele. Rinovirusurile umane (HRV) sunt agentul patogen viral principal în declanșarea AECOPD, iar infecția experimentală a furnizat noi dovezi semnificative în stabilirea unei relații cauzale între infecțiile virale și AECOPD.

Inhibitorii pompei de protoni (PPI), cei mai puternici supresori ai acidului gastric, sunt frecvent prescrise pentru BRGE izolat sau BRGE, complicând BPOC. A existat un progres în medicina respiratorie pulmonară prin faptul că IPP, pe lângă rolul lor bine dovedit în suprimarea acidului gastric, a apărut ca un instrument intervențional promițător în profilaxia și controlul simptomelor

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AECOPD. Această eficacitate nu se limitează la pacienții cu BPOC complicată de BRGE, deoarece IPP a redus, de asemenea, în mod independent și semnificativ riscul de a dezvolta AECOPD frecvent la cei cu BPOC în monoterapie, întârziind progresia bolii și îmbunătățind rezultatele clinice.

Deși studiile efectuate până în prezent cu privire la eficacitatea IPP au avut rezultate promițătoare, dovezile actuale sunt insuficiente pentru a determina în ce măsură utilizarea lor pe termen lung este sigură. Studiile multicentrice la scară largă sunt justificate pentru a evalua profilul lor de siguranță pe termen lung și rezultatele clinice.

Obiectivul acestui studiu este de a identifica un posibil rol al IPP în profilaxia și controlul simptomelor AECOPD.

Cuvinte-cheie

BPOC • AECOPD • BRGE • IPP • HRV

Introduction

“AECOPD, the “stroke of the lungs”, can be viewed as: a Semicolon or disease’s full-stop period, Triggering a catastrophic cascade, usually a Relapsing and Overwhelming event, acting as a Killer, needing Emergent treatment”.

Georgios Hillas et al. [1]

Chronic Obstructive Pulmonary Disease (COPD), the third leading cause of death worldwide, is a complex, heterogeneous, dynamic, unremitting, progressive, and treatable (but not curable) systemic condition, with pulmonary and extra-pulmonary manifestations. Exacerbations of COPD (AECOPD) are episodes of worsening of symptoms, abruptly interrupting the stable course of the disease and are indicative of an inexorable decline of lung function leading to substantial morbidity and mortality. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has updated its definition as: *“an event characterized by dyspnea and/or cough and sputum that worsen over < 14 days. AECOPD are often associated with increased local and systemic inflammation caused by airway infection, pollution, or other insults to the lungs”* [2].

Gastroesophageal Reflux Disease (GERD), a known comorbidity of COPD, is a common chronic, relapsing condition that carries a risk of significant morbidity and potential mortality from resultant complications. It has been defined, by the World Gastroenterology Organization, 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 definition of GERD, by the Montreal Consensus Group, is: *“a condition that develops when the reflux of stomach contents into the esophagus causes troublesome symptoms and/or complications”* [4]. Whereas GERD is known to aggravate COPD’s clinical status, the

mechanical changes caused by COPD may exacerbate GERD’s severity [5]. Understanding the consequences of their co-occurrence is of paramount importance.

COPD is usually associated with significant concomitant chronic diseases. The most common complication is an exacerbation, which is a *“catastrophic event during the clinical course of the disease”* and is acute in onset. AECOPD are a major cause of morbidity, mortality, and an economic burden. They may contribute to as much as 25% of lung function decline [6]. In addition, they have a significant detrimental impact on quality of life. In the natural history of disease, AECOPD may be triggered mainly by respiratory viral and bacterial infections. In the London COPD Cohort, it was concluded that they are not random events but cluster together in such a way that there is a high-risk period for recurrent exacerbation in the 8-week period after an initial exacerbation [7]. In the ECLIPSE study, the single best predictor of AECOPD was a history of exacerbation which became more frequent (and more severe) as the severity of COPD increased. People experiencing two or more exacerbations per year are regarded as having frequent exacerbations [8].

The **objective** of this study is to identify the possible role of PPI in prophylaxis and symptom control of AECOPD.

Literature Research

A comprehensive literature review was performed on electronic platforms: Pubmed, Scopus and Ovid, for publications in English, from 2000 to 2023. The following key words, in pairs, were used: “COPD AND: PPI”, “AECOPD AND: PPI”, “PPI Long Term Use AND: Safety”. The results were cumulated to get the final list of citations. Additionally, the retrieved articles were tracked down looking for other relevant studies or reviews. As a narrative review, no quality evaluation was performed.

The following research questions were formulated:

1. What is the link between GERD and COPD and what are the potential consequences of their co-occurrence?

2. Are PPI the most potent suppressants of gastric acid secretion?
3. What is the disease burden of AECOPD?
4. What is the etiology of AECOPD?
5. Is the present pharmacological management of AECOPD optimal? Could add-on PPI be of benefit?
6. If PPI were chosen as an interventional tool for AECOPD, their use would certainly be for long periods. How safe is their long-term use?
7. What are inappropriate prescribing and over-utilization of PPI?
8. What are the criteria for deprescribing (stopping??) PPI?

The Link Between GERD and COPD

The prevalence of GERD in people with COPD ranges from 19% to 78% compared to an average of 18% in controls [9]. The possible mechanisms of AECOPD are vagally mediated reflex bronchoconstriction and pulmonary micro-aspiration [10]. GERD is considered to be one of the causes of chronic cough, which is a common symptom of COPD [11]. In a randomized controlled trial, at the Jessenius Faculty of Medicine Slovakia, it was concluded that acidification of the esophagus acutely increases cough sensitivity in patients with GERD [12]. The resultant cough may increase the frequency of AECOPD [13]. In an observational Korean study on patients with COPD undergoing esophagogastroduodenoscopy, 50.9% were diagnosed with GERD.

Theophylline and LAMA use was significantly more common in those found to have GERD [14]. The use of bronchodilators (e.g., theophylline) and inhaled long-acting beta-agonists (LABA, e.g., 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 [15]. Thus, a component of GERD may be attributable to treatment of concomitant COPD. The increased central drive, flattening of the diaphragm, increased intra-abdominal and negative intrathoracic pressures, when present in patients with COPD, could favor the development of reflux [16]. In a nationwide population-based Taiwanese study, the COPD with symptomatic GERD cohort had a significantly greater risk of AECOPD than the COPD alone cohort [17].

With this background, it is tempting to postulate that reducing gastric acid secretion may lead to a reduction in AECOPD. Proton pump inhibitors (PPI), because of their inhibitory effects on gastric acid secretion, are the most commonly prescribed first-line therapy for those with GERD.

Are PPI Potent Suppressants of Gastric Acid Secretion?

The PPI are the most commonly prescribed and most consumed medications all over the world. They have been

licensed by the U.S. Food and Drug Administration (FDA) for treatment of GERD, peptic ulcer disease (PUD), 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) [18]. They selectively and irreversibly inhibit the proton pump that accomplishes the final step in acid secretion. They protect human gastric epithelial and endothelial cells against oxidative stress. It has been demonstrated that they prevent gastric mucosal injury by mechanisms independent of acid inhibition. However, this effect is invalidated in the presence of the heme oxygenase-1 (HO-1) inhibitor ZnBG. In a German study, it was found that the antioxidant defense protein HO-1 is a target of PPI in both endothelial and gastric epithelial cells [19].

Seven PPI are currently approved by FDA for use in various dosages and formulations, including enteric-coated tablets and gelatin capsules, delayed-release tablets and powdered forms for intravenous use. The initial PPI approved for use 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). Most are now available in generic forms. Omeprazole, esomeprazole and lansoprazole are also available over-the-counter in North America and Europe. However, in Japan, all PPI require a prescription [20].

Vimovo is a prescription combination drug product that contains PPI (esomeprazole magnesium) and naproxen [18]. Vonoprazan fumarate (Takecab), a novel potassium-competitive acid blocker, has been approved as mono therapy for GERD, as dual therapy (Vonoprazan, Amoxicillin) and as triple therapy (Vonoprazan, Amoxicillin, Clarithromycin) for *Helicobacter pylori*.

Based on a clinical trial, Hatlebakk et al concluded that for better acid suppression, the PPI should be taken before a meal [21], ideally first thing in the morning when taken once daily. If twice-daily dosing is employed, then a second dose is usually added approximately 30 minutes before dinner. When administered orally, PPI is rapidly absorbed and decreases gastric acidity by 80% to 95% [22]. For immediate acid suppression, there are intravenous formulations for lansoprazole, pantoprazole and esomeprazole. Of note, PPI does not show the tolerance phenomenon, even after long-term treatment [23].

Disease Burden of AECOPD

COPD is usually associated with significant concomitant chronic diseases. The most common complication is AECOPD which are a major cause of morbidity, mortality,

and an economic burden. In addition, they have a significant detrimental impact on the quality of life. In a Canadian study, Suissa et al concluded that the course of COPD involves a rapid decline in health after the second severe exacerbation and high mortality in the weeks following every severe exacerbation [24]. The frequent-exacerbation phenotype appeared to be relatively stable over a period of 3 years and was independently associated with a history of GERD, poorer quality of life, and elevated white-cell count [8]. In the Bergen COPD Cohort Study to identify predictors of AECOPD, a vicious circle affecting a large proportion of the patients was identified where one exacerbation predisposed to the next, leading to an ever-increasing disease burden [25].

The economic burden of AECOPD is of paramount importance. It has been estimated that recurrent AECOPD have significant impact on direct costs (increased use of drugs, emergency department visits and hospitalization) and indirect costs (absenteeism (loss of productivity due to sick leave) and presenteeism (loss of productivity due to reduced work capacity), early retirement or permanent reduction in work capacity) [26].

Etiology of AECOPD

Most AECOPD are associated with respiratory infections and, with advancement of scientific knowledge, both bacterial and viral infections (solely or in combination) have been found responsible. Virus detection during AECOPD, using PCR, has been found to vary from 22% to 60% [27]. Human rhinoviruses (HRV), the etiological agent of common cold, constitute the top viral pathogen in triggering AECOPD [28]. In a study conducted at The Medical University of Vienna, Austria, it was found that during national lockdown in the COVID-19 pandemic the transmission of nearly all respiratory viruses was halted with the exception of HRV. [29]. Previously they were considered “benign” causing only a mild upper respiratory tract infection “common cold”. But they are also found in the lower respiratory tract, specifically in those with AECOPD. There are some geographical differences. In most European studies they are the most common viruses, whereas in North America and Asia, the etiology is diverse [27]. There is also seasonal variation. Whereas the exacerbations in the northern and southern regions showed an almost two-fold increase in the winter months, no seasonal pattern occurred in the tropics [30]. Based on epidemiological data, a link has been suggested between AECOPD and virus infection as the co-occurrence is more common in the autumn and winter months. In a study in the UK, Hurst et al concluded that frequency of AECOPD was associated with an increased frequency of acquiring the common cold [31].

During AECOPD, the detection of respiratory viruses at a greater frequency than in stable COPD, the high levels of viral RNA/DNA in sputum samples, preceding common cold symptomatology and the seasonality of AECOPD coinciding with the seasonality of respiratory viral infections all support a role for respiratory viruses in AECOPD. Moreover, evidence favoring a causal relationship has been found in case-control studies. In a UK case control study, it was found that the IP-10 increased from baseline to exacerbation in HRV-positive exacerbations and correlated with sputum HRV load [32].

The role of respiratory virus infections in asthma (which shares many of the features of COPD including AECOPD), has been well established through experimental HRV infection which was carried out with an excellent safety record [33]. The interesting role of deficient type III interferon-lambda production in asthma exacerbations, identified in a UK study, led to the development of inhaled interferon- β and its therapeutic efficacy has been recognized [34]. This has led researchers to explore the possibility of experimental HRV infection in developing an identical model in COPD.

The virus challenge model in humans, also known as experimental HRV infection, has provided significant new evidence in establishing a causal relationship between virus infection and AECOPD. The promising results of a small pilot study of inoculation with a low dose of HRV in 16 subjects with COPD and thereafter, on a larger group of COPD patients together with a group of smokers without COPD (control) demonstrated that experimental infection in those with COPD can safely induce the typical clinical features of an AECOPD. Whereas all the study subjects were inoculated with the same dose of virus via the same route of inoculation, the post-inoculation virus loads in the COPD group were higher compared to the non-COPD group [27]. The increased post-inoculation virus load and the onset of symptoms indicating active viral replication occurring in the airways and the resolution of clinical symptomatology following virus clearance demonstrated a causal relationship between virus infection and AECOPD [27]. In a UK case-control study to evaluate experimental HRV infection as a model of AECOPD and to investigate the mechanisms of virus-induced exacerbations, a new model of AECOPD was developed that strongly supports a causal relationship between HRV infection and AECOPD. Moreover, virus-related production of interferons was impaired in broncho-alveolar lavage cells from patients with COPD as compared to those from controls [35].

Pharmacological Management of AECOPD: Present and Future

Since much of the morbidity, mortality and health care costs of COPD are attributable to AECOPD, reduction in their

frequency and severity should be a key therapeutic goal in management of COPD. The goals, set by GOLD-2023, are *“to minimize the negative impact of the current exacerbation and to prevent subsequent events”* [2].

Traditional pharmacotherapy includes antibiotics, inhaled bronchodilators, and steroids. The use of high doses of antibiotics, in the recent past, is based on the assumption that bacterial infection is the most common etiology. However, such use, without signs of infection, remains controversial [36]. The recommendation regarding duration of antibiotic therapy (5 to 7 days) originates from the use of levofloxacin 500 mg, which achieved clinical and bacteriological success regardless of the therapeutic course (5 or 7 days) [37]. It has been shown that inhaled therapies are poorly effective in preventing virus-induced exacerbations. [28]. There is strong evidence for the use of systemic steroids in severe AECOPD, as reported in the European Respiratory Society/American Thoracic Society consensus guideline[38]. In this clinical scenario, antiviral therapy has not been taken into consideration although viruses were frequently found in AECOPD, either as the primary infecting agent or as a co-factor.

Rhinoviruses, single-stranded (+) RNA viruses, a member of the family Picornaviridae, have more than 150 strains to date. Because of the large number of strains, antigenic heterogeneity and repeated unsuccessful attempts, development of a rhinovirus vaccine in near future appears to be unlikely. Under the circumstances, there is a dire need to find anti-viral therapies which can prevent exacerbations or reduce attack severity. What has been achieved so far? There is a long list of the products introduced but none has reached the established criteria for acceptance.

Arbidol (Umifenovir) is a non-nucleoside broad-spectrum antiviral drug which, in addition to inhibition of influenza virus, claims efficacy against a variety of other viruses including respiratory syncytial virus (RSV), parainfluenza virus, HRV, coxsackie virus (CV), adenovirus (ADV) in vitro and in vivo [39]. An open label and prospective study were conducted in Saint Petersburg State Medical University Russia, to assess its efficacy in the prevention of virus-induced exacerbations of bronchial asthma and COPD. Seasonal and post-exposure prophylaxis reduced the severity of COPD aggravations resulting in a decrease in the number of hospitalizations [40]. However, the safety and scientific validity of the studies, conducted so far, has not been evaluated by the FDA. Chinese researchers have advocated the unique synergistic antiviral effects of Shufeng Jiedu Capsules and Oseltamivir in AECOPD. Efficacy has been claimed against influenza A viral-induced acute exacerbations only. It has not gotten approval from the FDA. Additionally, WHO has downgraded Oseltamivir on drug lists because it is less cost-effective [41].

As a result of extensive research, PPI has emerged as a promising interventional tool in the management of AECOPD.

In addition to acid suppression, they have been found to have an impact on viral infections, notably that of HRV [42]. People who experience frequent AECOPD may have a high sensitivity towards respiratory viral infections or have poor ability to prevent viral replication [43], making PPI a viable treatment option.

Although not licensed for use in COPD, the acid suppressant effects of PPI play an important role in the management of AECOPD. Whereas COPD and GERD are mutually causal, forming a vicious circle [44], GERD is an independent risk factor for AECOPD [8]. PPI are first-line drugs for the treatment of GERD and their use in patients with COPD complicated by GERD may reduce the number of AECOPD, thus delaying disease progression and improving clinical outcomes. In The Copenhagen City Heart Study of 9,622 patients [45] and in an American single-center retrospective analysis of 1,445 patients [46], a protective effect of PPI against worsening airway obstruction was reported. A nationwide population-based Taiwanese study was conducted, using data from Taiwan's National Health Insurance Research Database, and enrolling 3,485 patients with COPD and symptomatic GERD and 13,938 patients with COPD alone. The use of PPI was associated with a lower risk of AECOPD and mortality in the patients with COPD and symptomatic GERD [17]. 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, was conducted. Patients with GERD or gastroduodenal ulcer were excluded. 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 a year in the PPI group was significantly lower than that in the control group [47].

Oxidative stress, defined as *“a disturbance in the balance between the production of reactive oxygen species (free radicals) and antioxidant defenses”* [48] arises as a result of endogenous antioxidant defenses being impaired and/or overwhelmed by the presence of re-active oxygen species (ROS). It is increased in patients with COPD particularly during AECOPD, accelerating disease progression, increasing comorbidities and amplifying AECOPD. It also causes corticosteroid resistance, increased autoimmunity, accelerated aging and cellular senescence [49]. In a study conducted in University of Mosul Iraq to explore the possible antioxidant capability of omeprazole and esomeprazole, they were found to confer a significant dual action in gastrointestinal protection by providing potent antioxidant properties in addition to their major role as acid-suppressant agents [50].

How Safe is Long-term Use of PPI?

When does PPI use become long term is an important question? The definition is seldom rationalized. The scoping review (*"preliminary assessment of potential size and scope of available research literature"*—Grant and Booth 2009) by Haastrup et al could not yield a conclusive answer. In most cases it was ≥ 1 year or ≥ 6 months [51]. According to the Guidelines of The UK Medicines & Healthcare Products Regulatory Agency (MHRA), it is ≥ 1 year [52].

The indications for long-term use need to be elaborated. Currently, long-term PPI use is approved for prevention and symptom control in GERD and Barrett's esophagus, as prophylaxis for NSAID-associated bleeding, and for pathologic hypersecretory conditions including Zollinger-Ellison syndrome [53].

As already mentioned, PPI are not licensed for use in GERD associated COPD. The proposed off-label use would be long-term (realistically for an unspecified period) necessitating a meticulous look at long-term PPI-associated adverse events (PAAEs). The FDA adverse event reporting system (FAERS), one of the largest databases, is a major source of such information [54].

PPI has an encouraging safety profile. Analysis of safety data from patients during the 12-year period of the SOPRAN study and the 5-year period of the LOTUS study, together with reported serious adverse events and changes in laboratory variables, revealed no major safety concerns during 5-12 years of continuous PPI therapy [55]. In a long-term, open-label trial to assess the safety and efficacy of continuous maintenance treatment with PPI for up to 15 years, there were also no identifiable safety concerns [56]. However, some recent long-term studies 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 [53]. The issues of inappropriate prescribing and over-utilization of PPI and deprescribing (as and when clinically indicated) are of paramount importance and are discussed in the next paragraphs.

Inappropriate Prescribing and Over-Utilization of PPI

Despite their dramatic effects in the prophylaxis and treatment of GERD, Barrett's esophagus and NSAID-induced gastroduodenal ulcers, uncertainty prevails over the safety of long-term PPI use. In chronic hypochlorhydria, the resultant malabsorption of calcium, magnesium, iron, B12 and other nutrients poses potentially serious outcomes. The FDA states 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). However, off-label use (taking for longer

periods than specified) is not uncommon and certainly poses risks.

Inappropriate PPI use, 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"* [57], is an issue of serious concern. In a cross-sectional Irish study to determine the extent and indications for PPI use in Irish acute medical wards appropriate prescribing was found in only 30% of cases [58]. 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 medications. Stress ulcer prophylaxis was the most common indication; the level of supporting evidence being poor [59]. In a German cross-sectional observational study, no justification for the recommendation for continued PPI could be identified in 54.5% of hospital discharge letters [60]. In another cross-sectional Danish study, on long term users of PPI, those with verified indications were only 27% [61].

What could be the reasons for these findings? According to Icelandic researchers, the clinical efficacy and excellent tolerability may be the explanation for excessive and inappropriate use of PPI [62]. Targownik argues that the absence of highly effective competing drug options for upper GI symptomatology compels prescribers to favor PPI over other options. [63].

Overprescribing in the elderly, for chronic use, is an issue of serious concern as studies have shown that PPI was not always prescribed with a clear indication. 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) [64]. In a study on full medication exposure in older hospitalized patients (age 84 ± 7 years) in a Scottish health board, inappropriate overprescribing was observed in 85.8% of patients prescribed PPI [65].

In a Danish nationwide drug utilization study PPI use was particularly prevalent in elderly: people over the age of 60 years who were 3.5 times more likely to be using PPI than those under 60 years [66]. 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 [67]. In a multicenter prospective study, overprescription of PPI was found in 73.9% of the elderly [68]. What conditions are linked with overprescription? Whereas cardiac and metabolic diseases and corticosteroid use were significantly associated with overprescription, esophago-gastric diseases were negatively associated with overprescription [68]. Undoubtedly, the misuse and overuse of PPI (e.g., poor indication, higher dose, long duration), in addition to economic implications,

contribute to polypharmacy and potential risks of drug interactions and untoward effects [62].

Deprescribing PPI

“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”.

AGA Clinical Practice Update on Deprescribing [69]

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” [70].

According to the Guidelines for Safe Use of PPI, endorsed by the All-Wales Medicines Strategy Group (AWMSG), the evidence base on the adverse effects from long-term use of PPI is increasing [71]. Moreover, older people may be more susceptible to the adverse effects of long-term PPI use [65].

Haastrup et al, however, in a review by the Danish Research Unit of General Practice, have suggested that merely the risk of adverse effects should not be a reason to withhold PPI from patients with a true indication. Realistically, unnecessary discontinuation should not be based simply on apprehension of poorly proven adverse effects [72]. 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 [73]. At present, the best approach is to reduce the dose to a minimally effective level. The All-Wales Medicines Strategy Group advises that long-term PPI prescriptions should be reviewed at least annually [71]. Reviewing policy will not only reduce prescribing costs but will potentially increase patient safety.

The AGA Clinical Practice Update 2022 argues that “*de-prescribing is an important strategy to lower pill burden while reducing real costs and theoretical risks*” [69]. The aim of deprescribing long-term PPI is, in most cases, to reduce polypharmacy and potential untoward effects.

Should one abruptly discontinue PPI or taper the dose? Very limited data are available on the proportion of long-term users who could discontinue PPI without relapse of symptoms. In a double-blind, placebo-controlled Swedish trial, discontinuation of PPI was successful in 27% of long-term (48 months) GERD patients [74]. Sudden discontinuation, after prolonged use, may result in “Rebound Acid Hyper-Secretion Syndrome” necessitating re-institution of the PPI [62]. Tapering could be a preferable option and consideration should be given to step-down

therapy in line with NICE guidance and PRN treatment [75]. According to the “*BEST PRACTICE ADVICE most patients with an indication for chronic PPI use who take twice-daily dosing should be considered for step down to once-daily PPI*” [69].

Where stopping 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 criteria used to review medication regimens in elderly people. [76].

Undoubtedly, efficacy of PPI in the prophylaxis and symptom control of AECOPD is very promising but they are not licensed for use in COPD. This is why “AGA Best Practice Advice” [77] and “AGA Clinical Practice Update” [69], do not advocate their long-term use in AECOPD, at present. However, general guidance could be sought from 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*” [69]. This could reasonably be applied to COPD where no justification for deprescribing seems likely. AGA’s Best Practice Advice 6 states :“*The dose of long-term PPI should be periodically reevaluated so that the lowest effective PPI dose can be prescribed to manage the condition*” [77]. Prescribers should discuss the rationale for deprescribing and involve patients in the decision [75].

Discussion

COPD is the third leading cause of death worldwide, the fifth-ranked cause of chronic disability, and a leading cause of emergency hospital admission. It is an increasing global health issue. Its prevalence increases as populations age, and it is usually associated with significant concomitant chronic diseases. Its commonest complication is an exacerbation which is acute in onset and the frequency of which increases with the severity of COPD. AECOPD are a major cause of morbidity and mortality, and an economic burden. In the UK, COPD costs around GBP 2 billion/year [78].

In view of the expense incurred in managing comorbidities, the costs are expected to rise globally. According to a report by the World Economic Forum and the Harvard School of Public Health, September 2011 on The Global Economic Burden of Noncommunicable Diseases, the global cost COPD management will rise to US\$ 4.8 trillion in 2030 [79].

Detection of respiratory viruses, during AECOPD, has been demonstrated at a greater frequency than in stable COPD. HRV is the top viral pathogen in triggering AECOPD, and experimental rhinovirus infection has provided significant new evidence in establishing a causal relationship between

the virus infection and AECOPD. It is a major advance 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. Interestingly, the efficacy is not limited to patients with COPD complicated by GERD. PPI also independently and significantly reduced the risk of developing frequent AECOPD, delaying disease progression and improving clinical outcomes.

Conclusion

Current evidence regarding the effectiveness of PPI in AECOPD has yielded promising results and is a major advance. Experimental rhinovirus infection in humans has paved the way for designing large scale multi-center clinical trials to establish a definite association between long term PPI use and the risk of serious adverse effects. However, it would be prudent to prescribe PPI at the lowest effective dose and only for as long as clinically indicated. The benefits of PPI, demonstrated to date, greatly outweigh the known risks and they have emerged as potent acid suppressants and promising anti-viral treatments and antioxidants: **Three in One.**

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Data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare no conflict of interest.

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