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Bringing stability to the COPD patient: clinical and pharmacological considerations for frequent exacerbators

Swati Gulati, M.B.B.S., M.S. and

Division of Pulmonary, Allergy, and Critical Care, Lung Health Center University of Alabama Birmingham (UAB). Address: 1900 University Blvd. Tinsley Harrison Tower, Suite 422, Birmingham, AL 35294, Phone: 205 934 5059, Fax: 205 934 1721

J. Michael Wells, M.D.

Division of Pulmonary, Allergy, and Critical Care, Lung Health Center University of Alabama Birmingham (UAB), Birmingham VA Medical Center, Birmingham, AL, USA. Address: 1900 University Blvd. Tinsley Harrison Tower, Suite 422, Birmingham, AL 35294, Phone: 205 934 6047, Fax: 205 9341446

Abstract

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are critical events associated with accelerated loss of lung function, increased morbidity, and excess mortality. AECOPD are heterogeneous in nature and this may directly impact clinical decision making, specifically in patients with frequent exacerbations. A “frequent exacerbator” is a sub-phenotype of COPD that is defined as an individual who experiences ≥2 moderate to severe exacerbations per year. This distinct subgroup has higher mortality and account for more than half of COPD-related hospitalizations annually. Thus, it is imperative to identify individuals at risk for frequent exacerbations and choose optimal strategies to minimize risk for these events. New paradigms for utilizing combination inhalers and the introduction of novel oral compounds provide expanded treatment options to reduce the risk and frequency of exacerbations.

The goals of managing frequent exacerbators or patients at risk for AECOPD are: 1) maximizing bronchodilation, 2) reducing inflammation, and 3) targeting specific molecular pathways implicated in COPD and AECOPD pathogenesis. Novel inhaler therapies include combination long acting muscarinic agents (LAMA) plus long acting beta agonists (LABA) show promising results compared to monotherapy or LABA inhaled corticosteroid (ICS) combination in reducing exacerbation risk among individuals at risk for exacerbations and among frequent exacerbators. Likewise, oral medications including macrolides and phosphodiesterase (PDE4) inhibitors reduce the risk for AECOPD in select groups of individuals at high risk for exacerbation. Future direction in COPD management is based on identification of various subtypes or “endotypes” and targeting therapies based on their pathophysiology. This review aims to describe the impact of AECOPD,

Correspondence to: J. Michael Wells.

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challenges posed by frequent exacerbators, and explores the rationale for different pharmacologic approaches to preventing AECOPD in these individuals.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death in the United States, reaching this rank in 2008- nearly a decade earlier than projected by Global Burden of Disease Study.[1] [2] Acute exacerbations of COPD (AECOPD) significantly alter the natural course of disease by accelerating decline in lung function and impact quality of life, mortality, and health care utilization[3] [4] [5] [6] [7]. Admissions for COPD exacerbations have an estimated in-patient mortality of 10% and 4-year mortality following an exacerbation can be as high as 45%.[8] These events also remain a major driver of COPD related health care cost, with estimated annual healthcare costs 9- to 10-fold greater for individuals who experience AECOPD as compared to non exacerbators, and these costs increase with frequency and severity of exacerbations.[2] [9]

Owing to its effects on patients' health status and its economic burden, preventing and mitigating the impact of AECOPD is the cornerstone of COPD management along with smoking cessation and symptom palliation. Here, we aim to review recent evidence behind pharmacological approaches to prevent exacerbations in conjunction with evolving understanding of exacerbation phenotypes. We performed a series of literature searches on PubMed for topics on frequent exacerbations and therapies including key searches using terms including "frequent exacerbation", "exacerbation", "COPD exacerbation", "exacerbation risk", "endotype", "long-acting beta-agonist"; "long-acting muscarinic antagonist", "combination inhaler", "inhaled corticosteroid", "macrolide", and "roflumilast."

2. Defining COPD exacerbations and frequent exacerbators

An acute exacerbation of COPD is defined as a sustained worsening beyond the normal day-to-day variation of the individual's condition from stable state that is acute in onset and warrants additional treatment. [9] [10] These events are typically characterized by the presence of one or more of three cardinal symptoms, including an increase or new onset dyspnea, sputum production, and sputum purulence plus the presence of supporting symptoms including wheezing, cough, fever, upper respiratory symptoms, tachypnea, or tachycardia. [11]

Infections are implicated in the majority of AECOPD, but other etiologies including exposure to noxious substances from the environment or allergens, occult cardiac ischemia, and pulmonary thromboembolism account for up to 30% of events. These complex interactions result in acute airway and lung parenchymal inflammation which lead to dynamic hyperinflation and symptom development.[12] [13] These interactions between the host and environment plus perturbations of many molecular biologic pathways help explain the heterogeneity of exacerbations. In turn, this heterogeneity accounts for some of the challenges clinicians face with treating these critical events.

The spectrum of COPD exacerbation ranges widely in its severity and frequency. Hurst et al defined the “frequent exacerbator” as an individual who experiences 2 or more moderate to severe exacerbations per year. The prevalence of frequent exacerbators was reported as 22% in GOLD 2, 33% in GOLD 3, and 47% in GOLD 4 COPD in the ECLIPSE study[14] and was reported as 41.4% for GOLD 1–2 and 58.6% for GOLD 3 and 4 COPD in a post-hoc analysis of POET-COPD.[15] In ECLIPSE, the authors identified include lower FEV_1, poor quality of life, increased serum white blood cell count, gastroesophageal reflux, and having a prior exacerbation as risk factors for the frequent exacerbator phenotype and demonstrated that frequent AECOPD occur in moderate as well as severe COPD.[14] However, determinants for changing from an “infrequent exacerbator” to a frequent exacerbator are not well understood. Thus, all individuals with any risk factor for becoming a frequent exacerbator should be considered at high risk for becoming frequent exacerbators. Three host-specific features that convey risk for frequent exacerbations include persistent inflammation, lung function and hyperinflation, and comorbid conditions.

2.1 Inflammation, endotypes, microbiota, and exacerbations

Due to the complex host-environmental interactions related to AECOPD, many pathways and molecular targets have been implicated in frequent exacerbations. For example, non-specific inflammatory markers such as interleukin (IL)-6 and IL-8 are elevated in the airways of frequent exacerbators measured during periods of clinical stability during exacerbations.[16] Likewise, elevated serum levels of c-reactive protein (CRP) measured in the recovery period is associated with shorter time until next exacerbation, implicating persistent inflammation in frequent exacerbations. [17]

Given the heterogeneity of COPD, new insights into its pathogenesis suggest that COPD is composed of multiple distinct disorders, or endotypes. An endotype is described as “a subtype of a condition, which is defined by a distinct functional or pathophysiological mechanism”.[18] The two well defined cell based endotypes in COPD patients are the neutrophilic endotype and the eosinophilic or Th2 endotype.[19] [20] The neutrophilic endotype is implicated in COPD and AECOPD pathogenesis due to its role in regulating host defense, inflammation, and protease release. Individuals with the neutrophilic endotype have elevated levels of persistent inflammation when in a non-exacerbating steady state and are associated with bacterial infection during AECOPD.[21] In fact, the majority of COPD exacerbations are neutrophil mediated and individuals who have neutrophil-predominant AECOPD have poorer outcomes compared to patients with eosinophilic exacerbations.[22] Thus, therapies targeting pathways implicated in neutrophil signaling are in nascent stages of development and have been tested in pre-clinical studies. These agents are discussed below in detail.

Although airway eosinophilia is not a distinct feature of COPD, a between 20–40% of individuals with COPD have increased sputum and blood eosinophil counts.[23] Airway biopsies taken at the time of exacerbation in this endotype have a 30-fold increase in the total number of eosinophils, suggesting a pathologic role in AECOPD.[24]This distinct COPD subgroup responds well to steroid treatment. [25] [26] Therapies for this endotype will be discussed below.

COPD exacerbations differ in pathophysiology based on the etiology of the event and response to the inciting element – through activation of inflammatory pathways, response to infectious triggers, or contributions of comorbid conditions including cardiovascular disease. Observational studies have proposed that the frequent exacerbator phenotype has increased viral susceptibility and experience a greater proportion of viral exacerbations than infrequent exacerbators.[27] [28] This distinction might be important in developing treatment strategies as viruses appear to stimulate more eosinophilic activity as compared to bacteria. [21]

Perturbations to the microbiome contribute to AECOPD risk by changes to the local microbiota as well as through increased susceptibility to acquisition of new strains of viral and bacterial infections. The lower airways are colonized by bacteria in 25–50% of individuals with COPD. [11] [29] Chronic colonization of the lower airways is an independent stimulus for airway inflammation and AECOPD. [30][31] Furthermore, changes to the airways microbiome occur at the onset of AECOPD.[32]

2.2 Airflow limitation, hyperinflation, and frequent exacerbations

Apart from persistent inflammation, airflow limitation is also a cardinal feature of COPD. Worsened lung function defined by lower forced expiratory volume in 1 second (FEV_1) places individuals at risk for frequent exacerbations. Conversely, exacerbations are associated with an accelerated loss of lung function. Recent work by Dransfield et al showed that each additional AECOPD increases the loss of lung function as measured by decline in FEV_1 by an additional 23mL/year as compared to non exacerbators. This phenomenon was most pronounced in patients with mild disease.[3] Other physiologic impairments of lung function, including resting and dynamic hyperinflation, also alter the risk for AECOPD. Frequent exacerbators have a higher degree of dynamic hyperinflation even in stable state. This not only contributes to symptoms of dyspnea, but also lowers the capacity to compensate for acute events.[33] [34] Bronchodilators help reduce dynamic hyperinflation by relieving small airway obstruction and hence “resetting” the exacerbation threshold.

2.3 The impact of comorbid conditions on exacerbation risk

Frequent exacerbators, now recognized to be a distinct phenotype in COPD, also have increased mortality. Since accelerated atherosclerosis and increased arterial stiffness has been demonstrated in COPD patients, efforts are now directed to understand the relationship between cardiovascular comorbidities and disease progression in this subgroup of COPD patients.[35] [36] Patel et al compared arterial stiffness, as a mark of cardiac risk in frequent COPD exacerbators to patients with infrequent exacerbations. This study noted that frequent COPD exacerbator had greater arterial stiffness than infrequent exacerbators and arterial stiffness increased acutely during COPD exacerbations, particularly with airway infection, and remained elevated for up to 8 weeks following resolution of the acute event.[37] These findings raise the concern that repeated exacerbations could result in cumulative cardiac injury, which can potentially explain increased mortality in these patients. Therefore, there is an increased interest in exploring effects of cardioprotective drugs on lung function and exacerbation rates in COPD patients. Angiotensin receptor blockers (ARBs) and HMG CoA reductase inhibitors (statins) were the first to be studied experimentally. ARBs failed to show

an improvement in lung function and statins failed to reduce exacerbation rates in these trials.[38] [39]

As compared to the results from the studies of ARBs and statins in mitigating AECOPD risk, findings from observational studies of beta blocker use in COPD are encouraging, with one study showing a reduction in AECOPD risk (RR 0.73; CI 0.60–0.90) in individuals receiving beta-blockers compared to participants who did not use beta blockers. This improvement in AECOPD risk was independent of the severity of lung function impairment and underlying cardiovascular disease. [40] In addition to cardioprotective effects, murine models have shown that chronic beta blocker administration decreases bronchoconstriction by upregulating airway beta receptors and decrease mucus production.[41] [42]. Based on these findings, a clinical trial investigating the impact of metoprolol on AECOPD risk is ongoing.[43]

2.4 The Clinical Challenge in Management of a Frequent Exacerbator

Despite important advances in therapeutic management of COPD, it remains a progressive disease. Although there have been several drugs recently approved for the treatment of COPD, the majority are inhaled therapies from the three main classes of medications used in treating COPD – namely long-acting beta agonists (LABA), long-acting muscarinic antagonists (LAMA), and inhaled corticosteroids (ICS). Of these classes and their combinations, few have shown benefits in reducing exacerbation frequency in clinical trials. Thus, approaches to ameliorating risk for AECOPD falls into these general categories; 1) maximizing bronchodilation through the use of long-acting bronchodilators, 2) reducing inflammation through the use of inhaled corticosteroids, chronic macrolide therapy, phosphodiesterase 4 (PDE4) inhibitors, and other compounds; and 3) applying precision medicine approaches through discovery and implementation of new treatments targeted at specific molecular pathways implicated in COPD and AECOPD pathogenesis to guide therapy. These approaches are covered below. While tobacco cessation, pulmonary rehabilitation, and supplemental oxygen use are vital in the management of COPD, these topics will not be covered in depth in this review.

3. Inhaled Long Acting Bronchodilators

Long acting bronchodilators remain cornerstone of COPD management. Long acting muscarinic antagonists (LAMA), long acting beta agonists (LABA), and combination LAMA/LABA therapies are the bronchodilators used in managing COPD. Bronchodilators play a pivotal role in preventing COPD exacerbations by improving baseline expiratory flow limitation and air trapping, hence increasing the difference between baseline air trapping and critical air trapping at which exacerbation occurs.[34] [44]

3.1 LAMA Monotherapy

Tiotropium is the most extensively studied LAMA and remains the most prescribed bronchodilator for COPD management. The results of trials evaluating LAMA monotherapy on AECOPD risk reduction are shown in Table 1. Niewoehner et al compared once daily tiotropium administered via dry powder inhalation (DPI) to placebo in a randomized

controlled trial of 1829 patients with moderate to severe airflow limitation. Tiotropium significantly decreased rate of exacerbations during 6-month treatment duration (27.9 % vs 32.3%, p<0.05).[45] This was followed by UPLIFT a randomized trial that showed a 14% reduction in exacerbation rate over 4 years in patients with moderate to severe COPD treated with tiotropium versus placebo. Tiotropium use was also associated with significant delay in time to first exacerbation with a median of 16.7 months (95% CI, 14.9 to 17.9) in tiotropium group versus 12.5 months (95% CI, 11.5 to 13.8) in the placebo group. [46] A recent post hoc analysis of UPLIFT categorized participants as frequent and infrequent exacerbators, as defined by Hurst et al, and found that daily use of tiotropium prolongs the time to first exacerbation (HR: 0.81; 95% CI: 0.74, 0.88; p <0.0001 and HR: 0.90; 95% CI: 0.82, 0.99; p=0.023) respectively and reduced the number of COPD exacerbations compared to placebo in infrequent (rate ratio: 0.79; 95% CI: 0.72, 0.86; p<0.0001) and frequent exacerbators (rate ratio: 0.88; 95% CI: 0.81; 0.95; p=0.0009) as compared to placebo. Interestingly, tiotropium also reduced the proportion of patients shifting from infrequent to frequent exacerbation group as compared to placebo.[47] Spiriva Respimat, an aqueous form of tiotropium, has similar efficacy to the dry powder formula in preventing exacerbations (HR 0.95; CI 0.93–1.03). [48] [49]

Since 2012, several new LAMA agents have been approved for maintenance therapy in COPD. Aclidinium bromide, umeclidinium bromide, and glycopyrronium bromide are comparable to tiotropium in regards to FEV_1 improvement over placebo [50] [51] [52][53] [54] [55]. Glycopyrronium reduced the risk of moderate and severe exacerbation by 31% as compared to placebo in GLOW-1 study over 26 weeks (hazard ratio 0.69, 0.50 to 0.95, p 0.023) and reduced AECOPD risk by up to 34% (p <0.0001) as compared to placebo over 52 weeks in GLOW-2 study [56] [57] Neither aclidinium nor umeclidinium have been associated with AECOPD risk reduction.

3.2 LABA Monotherapy

The role for LABAs in COPD management is well established, as LABAs improve lung function, quality of life, and reduce AECOPDs in patients with moderate-to-severe COPD. A meta-analysis has shown that LABA monotherapy reduces AECOPD events by 21% (CI 10%–31%).[58] However, there is limited data comparing the efficacy of LABA versus LAMA monotherapy in reducing AECOPD. POET-COPD is the largest randomized controlled trial designed to directly compare the efficacy of tiotropium versus salmeterol in preventing AECOPD in individuals with moderate to severe COPD. Tiotropium use increased time to first exacerbation by 42 days compared to salmeterol (187 days vs. 145 days), corresponding to a 17% reduction in risk with tiotropium (HR, 0.83; 95% CI, 0.77 – 0.90; P<0.001). Further, tiotropium significantly reduced the risk of moderate exacerbations as compared to salmeterol by 14% (HR, 0.86; 95% CI, 0.79 – 0.93; P<0.001) and severe exacerbations by 28% (HR, 0.72; 95% CI, 0.61 – 0.85; P<0.001).[59] The INVIGORATE trial compared the efficacy of indacaterol to tiotropium in individuals at high risk for exacerbation.[60] Both treatments offered comparable improvements in lung function, but tiotropium outperformed indacaterol in reducing exacerbation risk. Among individuals receiving tiotropium, the annualized rate of exacerbations was lower (rate ratio 0.73 versus 0.90; p<0·0001) and the time to first moderate exacerbation was longer by 20% (HR 1.20,

P=0.0012) compared to the indacaterol group. These results confirm findings from POET-COPD study despite the low rate of AECOPD in INVIGORATE.[60] Extrapolating from these findings, LABA monotherapy should not be used in frequent exacerbators and instead LAMA or combination inhaler therapies should be considered.

4. Inhaled Corticosteroids

ICS have been used for decades in managing COPD due to their anti-inflammatory effects and their clinically obvious benefit in asthma patients. Although combination therapy with LABA/ICS has shown to reduce exacerbation rates, the place of ICS monotherapy in COPD management is still debatable. Most of the data comes from observational studies, meta-analyses and systematic reviews of small RCT. Results from these trials should be interpreted with caution because of variation in exacerbation definitions and inclusion criteria between different trials. Agarwal et al conducted a systematic review and meta-regression of 11 RCT comparing ICS monotherapy with placebo in COPD patients. ICS use was associated with only modest benefit in preventing COPD exacerbations compared to placebo (18% relative risk reduction; rate ratio 0.82; CI 0.73–0.92) and no linear relationship was found between drug efficacy and level of lung function as measured by FEV_1.[61] This is in contrast to earlier meta-analyses which included smaller trials and showed significant benefit of ICS monotherapy in preventing COPD exacerbation in patients with severe lung disease (FEV^1<50%). [62–65]

ISOLDE, a randomized controlled trial, compared fluticasone to placebo and showed no differences in annual rate of FEV_1 decline but fluticasone use was associated with a 25% reduction in annual exacerbation rate as compared to placebo (p 0.026). However, it is unclear if patients in both the groups were receiving optimum COPD treatment (combination therapy with LAMA, LABA and SABA) at baseline.[66]

ICS use is associated with increased risk of pneumonia, which can further affect morbidity and mortality in frequent exacerbators. A population based cohort study following over 160,000 COPD patients for 18 years found that ICS use was associated with a 69% increase in the risk of serious pneumonia as compared to patients who were not using ICS. [67] These findings confirm observations from the TORCH trial where fluticasone containing regimens had a higher incidence of pneumonia as compared to placebo.[68]

Thus, the WISDOM trial evaluated the stepwise withdrawal of ICS in patients with severe but stable COPD who were receiving concomitant LABA and LAMA.[69] Participants in WISDOM were low risk for AECOPD. This trial showed that stepwise removal of ICS did not affect rates of moderate and severe exacerbation as compared to the group who continued ICS therapy, which aligns with the systematic review done by Agarwal et al.[69]. However, more studies are needed to evaluate the role of ICS in patients with frequent exacerbations. Thus it might be safe to withdraw ICS in COPD patients who are at low risk of exacerbations. These changes are reflected in the 2017 GOLD update.[70]

5. Combination Inhaler Therapies

There has been accelerated research in the past few years to develop LAMA/LABA as well as new LABA/ICS formulations based on the rationale of maximizing bronchodilation, reducing AECOPD risk, and improving medication compliance among individuals with COPD. The summary of the results for trials investigating combination inhalers on mitigating AECOPD risk are shown in Table 2.

5.1 LABA/ICS

The majority of studies evaluating the efficacy of LABA therapy in mitigating AECOPD risk have evaluated LABA in combination with ICS. Combination of salmeterol/fluticasone has shown to significantly reduce bronchial inflammation, as evidenced by reduction in CD45 leukocytes, CD8 and CD4 cells along with decrease in cells expressing genes for the pro-inflammatory mediators in bronchial biopsy specimens of patients treated with LABA/ICS combination versus placebo.[71] Strong clinical data favoring use of LABA/ICS to reduce AECOPD comes from TRISTAN study in 2003, a randomized controlled trial comparing salmeterol/fluticasone combination inhaler to each of salmeterol monotherapy, fluticasone monotherapy, and placebo in 1465 patients with moderate to severe COPD, chronic bronchitis, and at least one AE COPD per year for the 3 years prior to enrollment were included. All treatment groups had significantly reduced number of exacerbations as compared to placebo group at one year. The rate of AECOPD fell by 25% in the combination group, by 20% in the salmeterol group and 19% in the fluticasone group as compared to placebo and the effect was most pronounced in patients with FEV_1<50%. Overall, the mean rate of exacerbation per patient per year were 0.97 in combination group as compared to 1.30 in placebo group.[72] The TORCH study, another randomized controlled trial comparing salmeterol monotherapy, fluticasone monotherapy, combination salmeterol/fluticasone, and placebo in moderate to severe COPD validated these findings. Combination therapy with salmeterol/fluticasone reduced the annual rate of exacerbations as compared to placebo (0.85 vs 1.13), corresponding to a rate ratio of 0.75 (95% CI, 0.69 to 0.81; p<0.001) and a number needed to treat of four to prevent one exacerbation per year. [73] Similar findings were present for salmeterol monotherapy compared to placebo. There was a slight benefit for AECOPD risk reduction in salmeterol/fluticasone compared to salmeterol or fluticasone monotherapy. Szafranski et al conducted a similar trial comparing twice daily budesonide (320 μg) and formoterol (9 μg) combination in a single inhaler, budesonide (200 μg) alone, formoterol (4.5 μg) alone, or placebo over a 1-year period in individuals with a FEV_1<50% and who reported at least one severe AECOPD in the year prior to enrollment. Budesonide/formoterol reduced the number of severe exacerbations by 24% compared to placebo, by 23% compared to formoterol, and by 11% compared to budesonide suggesting a role for budesonide/formoterol combination in high risk patients. [74] A follow up study using similar design compared the efficacy of same dose of budesonide and formoterol combination to high-dose ICS (budesonide 400 μg), formoterol (9 μg) and placebo. LABA/ICS use prolonged time to first exacerbation and reduced exacerbation rate compared with placebo (23.6%) and formoterol (25.5%) but not with budesonide alone (13.6%). Monotherapy with either inhaler did not affect rate of exacerbation as compared to placebo. [75] Recently, the combination of vilanterol and

fluticasone was associated with 8.4% (CI 1.1–15.2, p 0.02) lesser rate of exacerbations compared to usual care in moderate to severe COPD.[76] Taken together, these data suggest that ICS/LABA combination therapy is warranted for risk reduction in COPD exacerbations and possibly frequent exacerbators. There are no head to head trials comparing different LABA/ICS combination inhalers on exacerbation rates. However, no differences in efficacy in FEV_1 response and safety were noted between salmeterol/fluticasone and formoterol/budesonide combinations in a small study.[77]

Despite this clear role of LABA/ICS in COPD, there has been a focused interest in identifying unique phenotypes where LABA/ICS may be more efficacious. Recent studies have identified a subset of COPD patients with significant eosinophilic airway inflammation, i.e. the eosinophilic endotype. Interestingly, these patients exhibit great response to inhaled LAMA/ICS or ICS inhalation therapy. Pavord et al conducted a pooled analysis of three trials with LABA/ICS combination to study if higher blood eosinophil count was associated with greater reduction in exacerbation frequency with LABA/ICS combinations. The trial populations were divided into two groups: <2% blood eosinophilia and ≥2% eosinophilia. Among patients with ≥2% eosinophils, LABA/ICS was associated with significant reduction in rate of AECOPD versus tiotropium in both INSPIRE and TRISTAN studies with an exacerbation rate ratio of 0.75 (CI 0.60 to 0.92, p=0.006) and 0.63 (CI 0.50 to 0.79, p<0.001) when compared to placebo respectively. However, there was no difference in exacerbation rate in the SCO30002 trial.[26] Pascoe et al made similar observations in a post hoc analysis from two RCTs using the same stratification. LABA/ICS combination therapy (vilanterol/fluticasone) reduced exacerbations by 29% compared with vilanterol alone (mean 0·91 versus1·28 exacerbations per patient per year; p<0·0001) in patients with eosinophil counts of ≥2% or higher, and by 10% (0·79 versus 0·89; p=0·2827) in patients with eosinophil counts < 2%, suggesting selective benefit of ICS in patients who have eosinophilic driven inflammation during AECOPD.[78]

5.2 LAMA/LABA

As opposed to LABA/ICS combination that has bronchodilatory and anti-inflammatory properties, LAMA/LABA only have bronchodilator activity.[79] However, LAMA/LABA combination may synergistically increase the therapeutic benefit by simultaneously affecting beta adrenergic and muscarinic receptors, even at submaximal doses. The first LAMA/LABA approved in the USA was umeclinidium-vilanterol after studies demonstrated improvements in lung function, exercise tolerance, and symptoms in patients with COPD.[80] [81] Improvements in lung function were greater among individuals treated with combination umeclidinium/vilanterol compared to fluticasone/salmeterol among patients with moderate-to-severe COPD who were at low risk for AECOPD[82]. Similar improvements in lung function were reported with the addition of umedlidinium to fluticasone/vilanterol therapy.[83] However, no trials have specifically looked at the effect of umeclidinium/vilanterol on exacerbation risk. Other LAMA/LABAs including indacaterol-glycopyrronium, tiotropium-olodaterol and glycopyrronium-formoterol have shown sustained improvements in FEV_1 and dyspnea when compared to placebo and usual care. However, evidence regarding their efficacy to reduce frequency of COPD exacerbation is sparse.[84] [85] [86]

The strongest evidence for LAMA/LABA use to prevent exacerbations comes from the FLAME trial which compared indacaterol/glycopyrronium to salmeterol/fluticasone in COPD patients at high risk for AECOPD as defined by having at least one exacerbation in the past year.[84] The combination of indacaterol/glycopyrronium was superior to salmeterol/fluticasone in reducing annual rate of exacerbation by 11% (rate ratio 0.89; 0.83 to 0.96; P=0.003). The indacaterol-glycopyrronium group also had a longer time to the first exacerbation than salmeterol-fluticasone group (71 days vs. 51 days, p <0.001) representing a 16% lower risk. A subgroup analysis of high-risk patients (classified as GOLD B and GOLD D) demonstrated that LAMA/LABA was most efficacious in preventing moderate to severe exacerbations with little impact on reducing mild events. Based on the results of FLAME, the GOLD 2017 COPD management guidelines now suggest that LABA/LAMA combination be used as first-line therapy for high-risk, i.e. GOLD B and D patients.[70]

6. Oral Agents

6.1 Macrolide Antibiotics

Macrolides have long been a mainstay in treatment of AECOPD and provide symptomatic relief, improve exacerbation free interval, and aid peak flow recovery [87] [11] [88]. In addition to anti-bacterial activity, macrolides also have immunomodulatory and anti-inflammatory properties.[89] [90] Because of these effects, macrolides have been extensively studied as agents to prevent exacerbations. Erythromycin was the first macrolide to reduce exacerbation frequency in COPD patients. Seemungal et al randomized 115 patients with moderate to severe COPD to either 250mg erythromycin twice daily versus placebo for 12 months. Exacerbation frequency was significantly reduced in the macrolide arm as compared to placebo arm, with a rate ratio of 0.648 (CI 0.489–0.859; P .003). The erythromycin group also had a longer median time to first exacerbation compared to placebo (271 vs 89 days, P 0.02).[91] Likewise, the MACRO study, a multicenter randomized controlled trial demonstrated that azithromycin (250mg/day) reduced exacerbation frequency compared to placebo when taken for a 1-year period. Individuals at high-risk for AECOPD defined as those who received systemic steroids or had an emergency room visit in the previous year due to AECOPD or who were on long-term oxygen therapy were included in the study[92]. Azithromycin decreased the frequency of exacerbations as compared to placebo (1.48 exacerbations per patient year vs 1.83, p <0.001) and improved the quality of life. A subgroup analysis further suggested that azithromycin treatment reduces sputum proline-glycine-proline (PGP), a pro-inflammatory chemokine implicated in COPD pathogenesis and progression, providing additional information on the anti-inflammatory mechanism of azithromycin. [93] A subsequent study evaluating the effect of daily azithromycin use in neutrophilic COPD showed that a reduction in exacerbation frequency was also accompanied with a reduction in sputum neutrophilia as well as IL-8 and bacterial load.[94] A sub group analysis of the MACRO trial suggested that chronic azithromycin therapy may be more efficacious in older individuals and mild to moderate COPD but less efficacious among current smokers.[95] The COLUMBUS trial evaluated the efficacy of azithromycin 500mg three times weekly versus placebo in reducing exacerbation frequency among frequent or “super” exacerbators defined as individuals who had three or more AECOPD within the prior year.[96] The authors found a significant risk reduction

among those randomized to azithromycin compared to placebo (rate ratio 0.58, CI 0.42–0.79; p 0.001). These results are summarized in Table 3. Studies have also compared "pulsed" antibiotics to continuous antibiotics and a recent meta-analysis of seven randomized controlled trials showed that use of continuous prophylactic macrolide showed significant reduction in exacerbation frequency whereas the use of pulsed prophylactic macrolide was associated with non-significant reduction in exacerbation frequency.[97] Macrolides are, however, pro-arrythmogenic and a large retrospective study showed that patients who took azithromycin for 5 days had an increased risk of cardiovascular death as compared to patients who took no antibiotics (Hazard Ratio 2.88; CI 1.79 to 4.63; p <0.001).[98] Moreover, hearing loss was more common in the azithromycin group in the MACRO study. Hence, caution must be exercised in selecting COPD patients for prophylactic macrolide treatment, keeping in mind its otologic and cardiovascular side effect profile.

6.2 Phosphodiesterase 4 inhibitor (Roflumilast)

Roflumilast is a second generation phosphodiesterase-4 (PDE4) inhbitor that promotes effective inhibition of chemotaxis, cytokine production *in vitro* and reduces the number of leukocytes in sputum samples of COPD patients. [99] [100] Roflumilast is the only oral anti-inflammatory medication indicated by the FDA to reduce exacerbation risk in patients with severe COPD associated chronic bronchitis and a history of excerbations as shown in Table 4. In a phase III randomized controlled dose ranging trial, roflumilast had a dose dependent reduction in exacerbation risk compared to placebo (1.03 events per year in 250 μg/day vs 0.75 events per year in 500 μg/day vs1.13 events per year in placebo). Roflumilast also led to a modest dose dependent improvement post bronchodilator FEV_1. [101] Following the encouraging results of this trial, two randomized controlled trials showed that roflumilast improved lung function in patients with moderate to severe COPD but had no impact on exacerbation risk in these groups as a whole. [102] [103] As the result of these findings, a post hoc analysis of COPD sub-phenotypes showed reduction of exacerbation frequency in patients with chronic bronchitis by 26.2% compared to placebo (p 0.001). However, patients receiving concomitant ICS experienced an 18.8% reduction in exacerbation risk compared to placebo whereas patients not using ICS exhibited no clinical benefit compared with placebo.[104] Based on these results, the REACT trial was designed to address the efficacy of coated-tablet formulation roflumilast in preventing exacerbations in high risk patients, including frequent exacerbators and in individuals receiving LABA/ICS maintenance therapy. This multi-national, randomized placebo-controlled study showed that the rate of moderate to severe exacerbation was 13.2% lower in the roflumilast group than in the placebo group (rate ratio 0.868; CI 0.753–1.002, p 0.0529) in frequent COPD exacerbators already on LABA/ICS inhaled therapy.[105] The RE2SPOND trial was designed to evaluate the efficacy of the non-coated roflumilast tablet formulation in individuals at high-risk for AECOPD despite combination therapy with LABA/ICS with or without LAMA. While roflumilast failed to reduce moderate and severe exacerbations in the overall population (rate ratio, 0.92; CI, 0.81–1.04; $P = 0.163$), roflumilast reduced the exacerbation rates in individuals with a history of more than three exacerbations and/or one or more hospitalizations in the prior year by 39% as compared to placebo (rate ratio, 0.61; 95% CI, 0.39–0.95; $P = 0.030$).[106]

Roflumilast is generally well tolerated and the adverse effects (AEs) are class specific for PDE4 inhibitors. The most common AEs include intractable diarrhea, nausea, weight loss, depression and insomnia. In the landmark trial by Calverely et al, rates of AEs and drug discontinuation were noted to be 67% and 14% respectively.[102] Other small retrospective studies have shown that the discontinuation rate of roflumilast can be as high as 49–84% related to these side effects.[107][108] However, most side effects occur within 4–12 weeks of initiation of roflumilast and are self-limited.[109] The side effect profile of roflumilast should always be weighed against the benefit in individual patients. In patients who are likely to benefit the most from roflumilast, correct education on the gastrointestinal and neuropsychiatric AEs is paramount.

6.3 Anti-oxidant and mucolytic agents

N-acetyl cysteine (NAC) is a therapeutic agent with mucolytic as well as potent antioxidant and anti-inflammatory properties. NAC has been postulated to ameliorate the acute inflammatory state during exacerbations because of its role as a free radical scavenger. The BRONCHUS trial evaluated the efficacy of NAC 600mg daily versus placebo on lung function and AECOPD risk among 523 individuals with moderate to severe COPD over a 3-year period.[110] Although BRONCHUS failed to demonstrate efficacy for either lung function improvement or mitigation of exacerbation risk, groups of investigators felt this was due in part to the relatively low dose of NAC used as well as the inclusion of low risk individuals in the trial. More recent studies have evaluated the use of higher dose NAC in subjects at higher risk for AECOPD, including frequent exacerbators. Zheng at al randomized 990 patients with moderate to severe COPD to NAC 600mg twice daily versus placebo for 1 year and found that NAC reduced AECOPD events compared to placebo (1.49 vs 1.6 events/year respectively, exacerbation rate ratio 0·78, CI 0·67–0·90; p=0·0011).[111] These findings were confirmed in a similar study (1.59 events/year in NAC 600mg twice per day versus 2.22 events/year in placebo, P=0.04) plus a longer time to first AECOPD among individuals treated with NAC. In both these studies, NAC was not beneficial in low risk or mild COPD patients, again emphasizing need to tailor COPD management based on heterogeneous subgroups.[112] A meta-analysis suggests that higher doses (>1200mg per day) may be required to prevent AECOPD among individuals with chronic bronchitis and COPD.[113]

Carbocysteine is a compound with mucolytic and anti-oxidant properties similar to those of NAC. The efficacy of carbocysteine was evaluated in a cohort of COPD patients with frequent exacerbations living in China. Compared to placebo, carbocysteine 1500mg/day reduced the number of exacerbations per year (1.01 events/year versus 1.35 events/year, P=0.004). [114] However, few study participants were receiving ICS containing therapies, limiting the generalizability of these findings to a broader population. Despite these limitations, both NAC and carbocysteine are relatively innocuous compounds and are well tolerated, event in frequent exacerbators.

7. Other measures

7.1 Vaccinations

Respiratory infections are important triggers for AECOPD.[27] Notably, 16–60% of viral induced AECOPD are associated with influenza infection.[115] [116] Influenza vaccinations reduce the risk of hospitalization from COPD exacerbation and improve mortality. Poole et al estimated that inactivated influenza vaccination reduced rates of AECOPD after 3 weeks following vaccination. There was no increase in early exacerbation due to the vaccine itself.[117] Despite clear indications for Pneumococcal vaccination in reducing the risk for community-acquired pneumonia in COPD, the efficacy of Pneumococcal vaccine preparations in preventing COPD exacerbation is less clear. Furumoto et al demonstrated fewer infectious exacerbations in COPD subjects in the first year following vaccinations among individuals with COPD who received both Pneumococcal and influenza vaccines compared to influenza vaccine alone (10.3% versus 26.3%, P=0.037).[116] The GOLD guidelines recommend both influenza and Pneumococcal vaccination for all COPD patients.[118]

7.2 Non-pharmacologic measures

Smoking cessation is one critical intervention that improves mortality in COPD patients and is the only intervention which affects the decline in lung function.[119] [120] Smoking cessation is associated with a reduced risk for AECOPD, and the risk reduction is directly proportional to the time since abstinence.[119] [121] Pulmonary rehabilitation (PR) is a non-pharmacological intervention that improves exercise capacity, dyspnea, and improves quality of life in patients with stable COPD.[122] PR is also efficacious in improving reducing hospital readmission, improving quality of life, and improving mortality if started within 30-days of hospitalization for AECOPD.[123] Thus, both of these interventions should be high priority in all COPD patients.

8. Novel Therapies and Future Directions

Given the complexity and heterogeneity of underlying pathophysiologic mechanisms in COPD and AECOPD, there is an increased inclination towards exploring therapeutic strategies targeted at specific molecular pathways or distinct endotypes. As mentioned above, eosinophilia has become a major target for precision medicine in COPD since the identification of eosinophilic endotype.[124] [125] [126] In addition to using LABA/ICS in this subgroup, various TH2 cytokines involved in eosinophilic pathways are now being evaluated as potential therapeutic targets in these patients. Interleukin-5 (IL-5) is a candidate cytokine as it regulates differentiation, proliferation, survival, and activation of eosinophils.[127] Benralizumab is an anti-IL-5 monoclonal antibody that significantly improved FEV_1 from baseline as compared to placebo (0.13 vs −0.06 L respectively; p 0.014). There was a non-statistically significant reduction in AECOPD rates by 31% in a sub group of patients with baseline blood eosinophil concentrations of 200 cells/μL or more by 31% who received benralizumab as compared to placebo. Results of this pre-specified subgroup analysis are encouraging and warrant additional trials in patients with predominantly eosinophilic

inflammation. (P=0.26). [128] Additional studies exploring the effect of other anti IL-5 and anti IL-13 therapies are underway. [129] [130].

Neutrophils are key mediators of inflammation in COPD and become the predominant cell type as disease progresses. Thus therapies targeting inhibition of neutrophil actions as well as downstream mediators in the signaling pathway are being developed. Chemokine receptors on neutrophils, including CXCR2, play a central role in chemotaxis and adhesion of neutrophils in lungs.[131] Development and testing of CXCR2 antagonists is in nascent stages, which by inhibiting migration and activation of neutrophils in lungs offers a potential target to prevent lung damage during AECOPD. Two selective CXCR2 receptors, MK-7123 and AZD5069 have been evaluated for their efficacy and safety profile in COPD patients. MK-7123 was studied at 3 drug concentrations (10mg, 30mg and 50mg) as compared to placebo and 50mg treatment dose significantly improved FEV_1 as compared to placebo. However, exacerbation rates were not significantly different in both the groups (29.9% vs 31.2%, HR 0.96; CI 0.64–1.44), though studies were not powered for this endpoint. Neutropenia, defined as absolute neutrophil count <1000/mm^3 developed in 11% patients in the study drug group as compared to1% in the placebo group after 6 months of treatment. AZD5069, an alternate CXCR2 antagonist, was well tolerated in a phase IIb dose ranging study. Although, there was a trend towards improvement in FEV_1 in the treatment groups as compared to placebo; the study was not powered to detect differences in lung function as an efficacy parameter. Neutropenia occurred in 7% patients in the intervention group. Despite reduction in neutrophil counts, higher rates of infections were not seen in study groups in both the trials as compared to placebo. [132] [133]

P38-mitogen activated protein kinase (MAPK) inhibition is another potential target for COPD patients. P38-MAPK mediates expression of inflammatory markers, such as tumour necrosis factor α, interleukin (IL)-1, IL-6 and IL-8, which lead to characteristic chronic lung inflammation in COPD and is over expressed in active smokers. PH-797804 is a novel p38-MAPK inhibitor which has shown to improve FEV_1 and dyspnea after 6 weeks of use as compared to placebo in patients with moderate to severe COPD. [134] However, another selective p38-MAP kinase inhibitor, losmapimod, failed to show any improvement in lung function as compared to placebo. [135] A post hoc analysis of this trial showed that losmapimod reduced exacerbation rate in subgroup of patients with <2% blood eosinophil count at baseline. [136] Due to lack of favorable results, further efforts for PH-797804 and losmapimod drug development are at hold. Therapeutically targeting specific endotypes is a novel approach and holds potential for bringing a paradigm shift in COPD management in the future.

As discussed above, chronic bacterial colonization contributes to the risk for AECOPD through altering host defense and modulating immune responses. Bacterial lysates, reconstituted mixtures of bacterial antigens present in the lower airways of individuals with COPD, act as immunostimulants through induction of cellular maturation, stimulating lymphocyte chemotaxis, and increasing opsonization when administered to individuals with COPD. [137] [138] [139] Small studies have shown mixed results in evaluating the efficacy of bacterial lysates in patients with COPD. A systematic review of 13 studies showed that the main treatment effect in preventing exacerbations was only found in smaller studies and

the combined analysis showed no difference between intervention and placebo group in reducing exacerbation frequency in COPD patients. [140] Most of these trials were done prior to the routine use of long-acting bronchodilators and ICS in COPD. However, the recent study by Braido et al. evaluated the efficacy of Ismigen, a bacterial lysate, in reducing exacerbations in individuals with moderate to severe COPD who were at high risk for exacerbations.[137] They found no difference in exacerbation rate between Ismigen and placebo or time to first exacerbation. However, in secondary analyses, they observed a longer time to subsequent exacerbation and fewer days hospitalized for severe AECOPD. In an open-label pre-post study, Koatz et al evaluated the utility of OM-85 bacterial lysate at reducing respiratory infections in a mixed population of participants with asthma, allergic rhinitis, and COPD who had ≥3 respiratory events in the preceding year.[141] The authors observed a 34% reduction in exacerbation frequency in the COPD subgroup (25 events versus 38 events in the previous year). These findings suggest a potential role for bacterial lysates in managing the frequent exacerbator, though larger and more robust clinical trials are needed to verify these findings.

Conclusions

The frequent exacerbator is a distinct COPD phenotype characterized by ≥2 exacerbations per year and poses a major healthcare burden due to increased costs, morbidity, and mortality. In clinical practice, identification of this subgroup is important for selecting appropriate management strategies aimed at reducing AECOPD risk and progression of lung function impairment. Approaches to mitigating AECOPD risk should include multi-modal interventions including smoking cessation, pulmonary rehabilitation, combination inhaler therapy, and the use of daily azithromycin or roflumilast. Although treatments for the frequent exacerbator will often include the use of many of these interventions, we recommend initiating therapy with a LAMA over a LABA for individuals who have previously had one exacerbation in the previous year. We recommend the use of LAMA/LABA over LABA/ICS as the next step in therapy for individuals who have an additional exacerbation despite LAMA monotherapy. For the frequent exacerbator, we recommend “triple therapy” with LAMA/LABA/ICS. As the phenotype of patients treated with “triple therapy” shifts from frequent to infrequent exacerbators, we recommend stopping ICS given the risk for pneumonia. Chronic macrolide or roflumilast therapy should be considered in individuals who remain high risk despite “triple therapy”. Often, the choice for oral therapy is dependent on the individual’s clinical phenotype and the side effect profile of the medication. Novel agents targeting specific pathways implicated in AECOPD are currently under development and show promise in early stage trials.

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Key Points

1. The frequent exacerbator is a distinct and important COPD phenotype occurring at all stages of lung function impairment and conveys increased risk for morbidity and mortality.
2. As compared to monotherapy, the use of combination inhalers have shown to reduce the risk and/or severity of AECOPD
3. Oral therapies including macrolide antibiotics, PDE4 inhibitors, and anti-oxidants reduce AECOPD risk in frequent exacerbators.

Table 1

LAMA monotherapy and AECOPD risk

Study	Study design, study drug and control arm	No. of patients	AECOPD as Inclusion criteria	Outcome (Primary vs Secondary)	Results	P value
Niewoehner et al (2005) [45]	RCT compared tiotropium 18μg to maintainence therapy including and/or combination of LABA, SAMA, ICS, Oral steroids, theophylline, or montelukast over 6 months	1829	No	**Primary outcome** Percentage of patients with a COPD exacerbation, % - Tiotropium vs control group Percentage of patients with hospitalization due to COPD exacerbation. - Tiotropium vs control group	 27.9 vs 32.3 7.0% vs 9.5	 0.037 0.056
UPLIFT trial (2008) [46]	RCT compared tiotropium 18μg to maintainence therapy including and/or combination of LABA, SABA, SAMA, ICS, Oral steroids, theophylline, montelukast or mucolytic agents over 4 years	5993	No	**Secondary outcome** Time to first exacerbation, months - Tiotropium vs control group Mean number of COPD exacerbations per patient per year - Tiotropium vs control group	 16.7 vs 12.5 0.73 vs 0.85	 Not reported <0.001
GLOW -1 D'Urzo et al (2011) [56]	RCT compared glycopyrronium bromide 50 μg to placebo over 26 weeks	822	No	**Secondary outcome** Annual rate of moderate or severe COPD exacerbation, % - Glycopyridinium vs placebo	 17.5 vs 24.2	 0.023
GLOW-2 Kerwin et a; (2012) [57]	Phase III RCT compared glycopyrronium bromide 50 μg to Placebo and open-label tiotropium groups over 1 year	1066	No	**Secondary outcome** Rate of COPD exacerbations per year in the 52-week treatment period Glycopyyronium vs Placebo	 0.54 vs 0.80	 0.003
POET-COPD Fabbri et al (2011) [59]	RCT compared tiotropium 18μg to salemeterol 50 μg over 1 year	7384	Yes, ≥1 AECOPD within the previous year	**Primary outcome** Annual rate exacerbation of COPD - Tiotropium vs salmeterol	 0.64 vs 0.72	 0.002

RCT: Randomized controlled trial, LABA: Long acting beta agonists; SAMA: Short acting anti-muscarinic agents; SABA: Short acting beta agonists; ICS: Inhaled corticosteroids; AECOPD: Acute exacerbation of COPD; FEV_1: Forced expiratory volume in 1 second

Table 2

Combination LABA/ICS or LABA/LAMA for Reducing Exacerbation Risk

Study	Study design, study drug and control arm	No. of patients	AECOPD as Inclusion Criteria	Outcome (Primary vs Secondary)	Results	P value
TORCH Calverley et al (2007) [73]	RCT compared salmeterol 50μg, fluticasone propionate 500μg and salmeterol 50μg/fluticasone propionate 500μg combination to placebo over 3 years	6184	No	**Secondary outcome**		
				Frequency of exacerbations (per year)		
				-Combination regimen vs placebo	0.85 vs 1.13	<0.001
				-Salemeterol vs placebo	0.97 vs 1.13	<0.001
				-Fluticasone Furoate vs placebo	0.93 vs 1.13	<0.001
INVIGORATE McBryan et al (2013) [60]	Non inferiority RCT compared indacaterol 150 μg to tiotropium 18 μg over 1 year	3444	No	**Secondary outcome**		
				Annualized rate of COPD exacerbations		
				-Indacterol vs Tiotropium	0.90 vs 0.73	<0.0001
Vestbo et al (2016) [76]	RCT compared inhaled combination of fluticason furoatee 100μg and vilanterol 25 μg to “usual care group” (COPD maintenance medication including LABA, ICS and LAMA) over 1 year	2802	Yes, ≥1 AECOPD/year in the previous 3 years before enrollment	**Primary outcome**		
				Mean annual rate of moderate or severe exacerbations		
				-Combination group vs usual–care group	1.50 vs 1.64	0.02
TRISTAN Calverley et al (2003) [72]	RCT compared salmeterol 50 μg, Fluticasone propionate 500 μg And salmeterol 50 μg/fluticasone propionate 500 μg combination to placebo over 1 year	1465	Yes, ≥1 AECOPD/year in the previous 3 years before enrollment	**Secondary outcome**		
				Mean number of exacerbations per patient per year		
				-Salmeterol vs placebo	1.04 vs 1.30	0.0027
				-Fluticasone vs placebo	1.05 vs 1.30	0.0033
				-Combination therapy vs placebo	0.97 vs 1.30	<0.0001
Szafranski et al (2003) [74]	RCT compared budesonide 200 μg, formoterol 4.5 μg and budesonide 160 μg/formoterol 4.5 μg combination to placebo over 1 year	812	Yes, ≥1 severe AECOPD within previous 2 to 12 months	**Primary outcome**		
				Mean exacerbation rates per patient per year		
				-Formoterol vs placebo	1.84 vs 1.87	0.895
				-Budesonide vs placebo	1.59 vs 1.87	0.224

Study	Study design, study drug and control arm	No. of patients	AECOPD as Inclusion Criteria	Outcome (Primary vs Secondary)	Results	P value
				-Combination therapy vs placebo	1.42 vs 1.87	0.035
Calverley et al (2003) [75]	RCT compared formoterol 9 μg, budesonide 400 μg and budesonide/formoterol 320/9 μg combination to placebo over 1 year	1022	Yes, ≥1 AECOPD in the previous 12 months	**Primary outcome**		
				Time to first exacerbation, in days		
				-Formoterol vs placebo	154 vs 96	0.901
				-Budesonide vs placebo	178 vs 96	0.512
				-Combination therapy vs placebo	254 vs 96	0.006
				Secondary outcome		
				Mean number of exacerbations per patient per year		
				-Formoterol vs placebo	1.85 vs 1.80	0.828
				-Budesonide vs placebo	1.60 vs 1.80	0.308
				-Combination therapy vs placebo	1.38 vs 1.80	0.029
FLAME Wedzicha et al (2016) [84]	RCT compared indacaterol 110 μg/glycopyrronium 50 μg combination (IG) to salmeterol 50 μg/fluticasone 500 μg combination (SF) over 1 year	3362	Yes, ≥1 AECOPD during the previous year requiring oral steroids	**Primary outcome**		
				Annual rate of all COPD exacerbation		
				-IG vs SF	3.59 vs 4.03	0.003
				Secondary outcome		
				Time to first exacerbation, days		
				- IG vs SF	71 vs 51	<0.001
				Annual rate of moderate or severe COPD exacerbation		
				-IG vs SF	0.98vs 1.19	<0.001
				Time to moderate or severe exacerbation, days		
				-IG vs SF	127 vs 87	<0.001

RCT: Randomized controlled trial, LABA: Long acting beta agonists; LAMA: Long acting anti muscainic agents, ICS: Inhaled corticosteroids; AECOPD: Acute exacerbation of COPD; FEV_1: Forced expiratory volume In 1 second

Table 3

Chronic Macrolide and AECOPD Risk

Study	Study design, study drug and control arm	No. of patients	AECOPD as Inclusion Criteria	Outcome (Primary vs Secondary)	Results	P value
Seemungal et al (2008) [91]	RCT compared erythromycin 250 mg twice daily to placebo over 12 months	109	No	**Primary outcome**		
				Median exacerbation frequency, n(IQR)		
				-Erythromycin vs placebo	1(1.00,2.00) vs 2 (0.25,3.75)	0.006
				Median Duration of exacerbation, days (IQR)		
				-Erythromycin vs placebo	9 (6,14) vs 13(6,24)	0.0036
MACRO Albert RK et al (2011) [92]	RCT compared azithromycin 250mg daily to placebo over 1 year	1130	Yes, ≥1 AECOPD in the previous year	**Primary outcome**		
				Time to the first acute exacerbation of COPD, days		
				-Azthromycin vs Placebo	174 vs 266	<0.001
				Rate of acute COPD exacerbation of COPD per patient-year		
				-Azthromycin vs Placebo	1.48 vs 1.83	0.01
COLUMBUS Uzun et al (2014) [96]	RCT compared azithromycin 500mg thrice weekly to placebo over 1 year	92	Yes, ≥3 AECOPD in the previous year	**Primary outcome**		
				COPD exacerbation rate per patient per year		
				-Azithromycin vs placebo	1.94 VS 3.22	0.003
				Secondary outcome		
				Time to first exacerbation, days		
				-Azithromycin vs placebo	130 vs 59	0.001
				OR for hospital admission due to acute COPD exacerbation in 2 groups	OR 1.34, 95% CI 0.67–2.70	0.41

RCT: Randomized controlled trial, AECOPD: Acute exacerbation of COPD; OR: Odds ratio; IQR: Interquartile range

Table 4

Roflumilast and AECOPD Risk Reduction

Study	Study design, study drug and control arm	No. of patients	AECOPD as Inclusion Criteria	Outcome (Primary vs Secondary)	Results	P value
Rabe et al (2005) [101]	RCT compared Roflumilast 250 μg and Roflumilast 500 μg to placebo over 24 weeks	1411	No	**Secondary outcome** Mean number of COPD exacerbations per patient -Roflumilast 250 μg vs placebo -Roflumilast 500 μg vs placebo	 1.03 vs 1.13 0.75 vs 1.13	 0.0029, one sided for Roflumilast vs placebo
Calverley et al (2009) [102]	2 RCTs (M2-124 and M2-125 study groups) compared Roflumilast 500 μg to placebo over 1 year	3091	Yes, ≥1 recorded AECOPD in the previous year	Rate of moderate or severe exacaerbation per patient per year -Roflumilast 500 μg vs placebo	 1.14 vs 1.37	 0.0003
Fabbri et al (2009) [103]	2 RCTs, M2-127 and M2-128 study groups, compared roflumilast 500 μg + salmeterol 50 μg and Roflumilast 500 μg + Tiotropium 18 μg respectively to placeb oover 24 weeks each	935	No	**Secondary outcome** Rate of COPD exacerbations per patient per year -Roflumilast + Salmeterol vs placebo -Roflumilast + Tiotropium vs placebo Median time to first (mild, moderate or severe) exacerbation, days -Roflumilast + Salmeterol vs placebo -Roflumilast + Tiotropium vs placebo Median time to first moderate or severe exacerbation, days -Roflumilast + Salmeterol vs placebo -Roflumilast + Tiotropium vs placebo	 1.9 vs 2.4 (RR 0.79) 1.8 vs 2.2 (RR 0.84) 53 vs 47 (HR 0.9) 50 vs 37 (HR 0.7) 83 vs 71 (HR 0.6) 80.5 vs 74.5 (HR 0.8)	 0.14 0.35 0.27 0.026 0.006 0.19
REACT Martinez et al (2015) [105]	RCT compared roflumilast 500 μg to placebo over 1 year	1945	Yes, ≥2 AECOPD in the previous year.	**Primary outcome** Rate of moderate to severe COPD exacerbation per patient per year		

Study	Study design, study drug and control arm	No. of patients	AECOPD as Inclusion Criteria	Outcome (Primary vs Secondary)	Results	P value
				- Roflumilast vs placebo	0.74 vs 0.92 (RR 0.80)	0.007
				Median time to first moderate to severe exacerbation, days		
				- Roflumilast vs placebo	103.5 vs 111.5 (HR 0.91)	0.22
				Median time to second moderate to severe exacerbation, days		
				- Roflumilast vs placebo	197 vs 190 (HR 0.79)	0.027
				Secondary outcome		
				Change in post-bronchodilator FEV_1 from baseline at 52 weeks, ml		
				- Roflumilast vs placebo	52 vs -4	<0.0001
RE^2SPOND Martinez et al (2016) [106]	RCT compared Roflumilast 500 μg to placebo over 1 year	2354	Yes, ≥2 AECOPD and/or hospitalizations in the previous year	**Primary outcome**		
				Rate of moderate or severe COPD exacerbations per patient per year		
				- Roflumilast vs placebo	1.17 vs 1.27 (RR 0.92)	0.163

RCT: Randomized controlled trial; AECOPD: Acute exacerbation of COPD; FEV_1: Forced expiratory volume In 1 second; HR: Hazard ratio; RR: Rate ratio