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REVIEW

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Update on the pharmacological treatment of chronic obstructive pulmonary disease

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ABSTRACT

Introduction: Chronic obstructive pulmonary disease (COPD) is a common syndrome associated with smoking and environmental exposures coupled with genetic susceptibility. Recent major advancements in the treatment of COPD patients have become available.

Areas covered: New data on the role of classic bronchodilators, including short-acting and long-acting beta2-agonists and anti-muscarinic antagonists, in the treatment of COPD patients are discussed. Data promoting a more targeted approach to inhaled and systemic corticosteroid use in COPD are reviewed. Phosphodiesterase (PDE) inhibitors, including the recently approved PDE 3/4 inhibitor inhaled ensifentrine, are noted. Selective use of antibiotics can play a role in complex COPD patients. COPD patients with evidence of asthma-COPD overlap syndrome and type-two lymphocytic inflammatory-mediated airway constriction appear to respond to biologics, particularly the anti-IL-4/IL-3 antagonist monoclonal antibody, dupilumab.

Expert opinion: New therapeutic options have made the approach and treatment of the COPD patient much more complicated. These options tend to be very expensive. Attention to identifying the endotype and phenotype will help direct the pharmacotherapy.

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COPD; bronchodilators; beta2-agonists; anti-muscarinic antagonists; corticosteroids; ensifentrine; macrolide antibiotics; dupilumab

1. Introduction

Chronic obstructive pulmonary disease (COPD) is the consequence of environmental exposures (cigarette smoking and air pollution) and genetic susceptibility. It is potentially both progressive and debilitating but is also preventable by controlling environmental exposures [1]. COPD results in exhaled airflow limitation or air trapping that is not fully reversible. As a clinical syndrome, COPD has variable elements of reversible airway disease, emphysema, and bronchitis with infections and/or excessive sputum production [2]. COPD continues to increase its ranking as a cause of death globally, most recently reaching the third leading cause of death with 3.23 million deaths attributed to it in 2019 [1].

1.1. Prevalence

A systematic review and meta-analysis using 60 papers and 127,598 subjects found that the prevalence of post-bronchodilator airway obstruction was 12.6% (10.91–13.40%) [3]. Pooled prevalence of COPD in this 2019 study was 15.7% (13.80–18.59%) in men and 9.93% (8.73–11.13%) in women. Some countries like the Kingdom of Saudi Arabia have seen a 49% increase in the prevalence of COPD in the population between 1990 and 2019 [4]. A more recent systematic review and meta-analysis used 42 studies and found the overall prevalence of COPD in people aged 40 years and older to be 12.64% (95% confidence interval (CI) 10.75–14.65%) to 7.38% (95% CI 5.47–9.55%) depending on the diagnostic criteria used [5]. In this study, men also had a higher prevalence of 15.47% (95% CI 12.22–19.02%) versus 8.79% (95% CI 6.94–10.82%) for women. Increased tobacco smoking in women from developed countries and the disproportionate exposure to indoor pollutants such as biomass burning in women from less developed countries have increased the prevalence of COPD in women in the 21st century, but some evidence suggests women may in fact be more susceptible to tobacco smoke than men [6].

1.2. The burden of COPD

A recent evaluation of the burden of COPD in the United States (US) included 4,135 COPD patients and 86,021 people without COPD [7]. Using 2019 US dollars, the COPD-attributed medical cost after adjustments was estimated to be $31.3 billion. They further estimated that by 2029, the costs would essentially double to $60.5 billion [7].

COPD often goes undiagnosed until it is advanced resulting in underestimating its true clinical and societal burden [8]. COPD exacerbations result in increased healthcare use, work absenteeism, and reduced productivity. Studies on mortality have ranged from hazard ratios (HR) of 4.3 (95% CI, 2.8–6.7) for death from respiratory causes to a HR of 2.0 (95% CI, 1.8–2.3) for death of any cause in Denmark [9]. An analysis of US data found that even in patients with undiagnosed COPD, an increased HR for death over 20 years was 1.23 (95% CI, 1.08–1.40) compared to those without

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Article highlights

- Treatment options for the COPD patient continue to evolve and become more complicated.
- In addition to inhaled short- and long-acting anti-muscarinics and beta2-agonists, inhaled corticosteroids appear to provide excellent treatment to the COPD patient with elevated eosinophils.
- Phosphodiesterase (PDE) inhibitors have a long history of use in COPD treatment but an inhaled PDE 3/4 inhibitor ensifentrine has recently been approved by both EMA and FDA and adds an additional therapeutic option.
- The asthma-COPD overlap syndrome or phenotype is frequently a type 2 lymphocyte inflammatory-mediated airway constriction process and monoclonal antibody (MAB) therapies improve outcomes in some patients. The anti-IL-4/IL-13 antagonist MAB dupilumab is thought to be effective in COPD patients with elevated eosinophilia.

COPD [10]. In 2023, recently released data suggests that death rates from lower respiratory disease decreased by 12.5% but still remained the fourth leading cause of death in the United States [11,12]. Exacerbations of COPD predict higher mortality risk [13]. This has resulted in a call for COPD management to be centered around reducing mortality and COPD exacerbations [13].

Using the Swedish national register (1997–2018) of all residents between 50 and 90 years-old, patients with a diagnosis of COPD were evaluated [14]. Of the 2,706,814 persons in the register, 8.3% had COPD. The investigations used a nested case-control with 223,945 COPD cases and 1,062,731 controls. COPD patients had increased risks for chronic heart failure (odds ratio (OR) = 3.25, 95% CI 3.20–3.30), peripheral arterial disease (OR = 3.12, 95% CI 3.06–3.18), and lung cancer (OR = 12.73, 95% CI 12.12–13.37). After the diagnosis had formally been made, an increased risk of depression was also found (HR = 2.58, 95% CI 2.53–2.64). Interstitial lung disease, emphysema, bronchiectasis, osteoporosis, and cardiovascular events have also been associated with COPD [15–17].

1.3. Therapy for COPD

This paper will focus on the pharmacotherapy used in treating COPD patients with an emphasis on newer agents. The frequently updated Global Initiative for Chronic Obstructive Lung Disease (GOLD) is a strategy document for the diagnosis, treatment and management of COPD patients and offers a comprehensive review of available treatments of COPD [18]. This review is limited to pharmacotherapy but this in no way downplays the importance of non-lung pharmacological directed approaches such as smoking cessation, airway valves, pulmonary rehabilitation, nutrition, oxygen therapy, and general lifestyle interventions in the comprehensive treatment of COPD [19–22].

2. Bronchodilators

Inhaled bronchodilators such as beta2-agonists and anti-muscarinics are a cornerstone of treatment for airway diseases, including COPD. Despite multiple new therapies, inhaled bronchodilators remain integral in the management of COPD in alleviating symptoms, improving lung function, and decreasing the rate of exacerbations. Inhaled beta2-agonists have been shown to improve forced expiatory volume in 1 second (FEV1), reduce dynamic hyperinflation, improve specific total airway resistance, improve exercise tolerance, and improve dyspnea and health-related quality of life scores. [18,23,24]. In this review, recent advancements and data on bronchodilators are presented. Table 1 provides a comprehensive summary of inhaled bronchodilators.

The relationship of frequency of dosing to adherence has clearly been shown to be an inverse relationship with increasing frequency for oral agents [25]. The relationship of frequency of required inhaler dosing and adherence is less clear in COPD patients [25]. Once-a-day ICS/LABA/LAMA inhaler in COPD patients was shown to be non-inferior to twice-a-day ICS/LABA plus once-a-day LAMA [26]. Once-a-day ICS/LAMA/LABA inhaler use in COPD has been shown to have significantly improved adherence compared to multiple-inhaler triple therapy [27]. A large study that included both asthma and COPD patients demonstrated that 80% or greater adherence was seen in the 1,791 COPD patients given once-a-day medication compared to twice-a-day inhalers (54.8% vs 38.6%, $p < 0.001$) [28]. Inhaler adherence even with the use of once-a-day inhalers remains a problem.

2.1. Beta2-agonists

Long-acting beta2-agonists (LABAs), such as formoterol and salmeterol, provide sustained bronchodilation by stimulating beta2-adrenergic receptors on airway smooth muscle cells, leading to the activation of adenylate cyclase and subsequent increase in cyclic AMP levels, which relaxes bronchial smooth muscle [18]. This relaxation causes the airway passages to widen, reducing airway resistance and facilitating easier ventilation [18]. Inhaled LABAs have also been shown to simulate airway cilia improving ciliary movement [29]. Beta2-agonists are categorized by the length of their clinical effect; inhaled short-acting beta2-agonists (SABA) and long-acting beta2-agonists (LABA) are major classifications.

While inhaled and targeted to the lung, beta2-agonists can lead to off-target effects, including tremors, hypokalemia, and cardiac arrhythmia [30]. Identifying the causality of arrhythmias is challenging, as cardiovascular disease is more commonly observed in patients with COPD independent of beta2-agonist medications [31]. Patients diagnosed with COPD are significantly more likely to have atrial fibrillation/flutter and ventricular tachycardia than those without COPD [32]. A 2015 meta-analysis demonstrated patients with COPD were over twice as likely (odds ratio (OR) 2.46; 95% CI 2.02–3.00) to develop cardiovascular disease when compared to matched cohorts, highlighting the need for careful attention to cardiac disease and risk in patients with COPD [33]. Despite these data and up to a third of patients with COPD dying of cardiac disease, a 2022 Canadian cohort demonstrated the exact opposite. Compared to a matched non-COPD cohort, patients with COPD achieved guideline-directed cardiac risk factor monitoring and management [34]. While some trials suggest an association between the use of LABAs and cardiovascular

Table 1. FDA-approved long-acting beta2-agonist and anti-muscarinic inhaled medications, including common brand names and combination inhalers.

Drug Class	Drug	Delivery Options	Half-Life (hours)	Time of Peak Plasma (min)	Monotherapy Brand Name	Combinations
Beta-Agonists	formoterol	MDI, neb, DPI	10 to 14	60 to 180	Performist, Foradil	budesonide (Symbicort*/Breyna*), mometasone (Dulera*), budesonide/glycopyrrolate (Breztri), glycopyrrolate (Bevespi), aclidinium (Duaklir Pressair)
	arformoterol	Neb	26	30 to 180	Brovana	NA
	vilanterol	DPI	21	10		fluticasone/umeclidinium (Trelegy Ellipta*), umeclidinium (Anoro Ellipta), fluticasone (Breo Ellipta*)
	indacaterol	DPI	40-56	15	Arcapta Neohaler	glycopyrrolate (Utibron Neohaler)
	olodaterol	SMI	7.5	10 to 20	Striverdi Respimat	tiotropium (Stioloto Respimat*)
	salmeterol	MDI, DPI	5.5	20	Serevent Diskus*	fluticasone (Wixela*/AirDuo RespiClick*/Advair*)
Anti-Muscarinics	tiotropium	SMI, DPI	25	5 to 7	Spiriva Respimat*, Spiriva Handihaler*	olodaterol (Stioloto respimat)
	revefenacin	Neb	22 to 70	14 to 41	Yuperli	NA
	glycopyrrolate	Neb, MDI, DPI	33 to 53	5	Lonhala Magnair, Seebri Neohaler	indicaterol (Utibron Neohaler), budesonide/formoterol (Breztri), formoterol (Bevespi)
	aclidinium	DPI	5 to 8	10	Turdoza Pressair	formoterol (Duaklir Pressair)
	umeclidinium	DPI	11	5 to 15	Incruse Ellipta	vilanterol (Anoro Ellipta), fluticasone/vilanterol (Trelegy Ellipta*)

MDI = metered dose inhaler; DPI = dry powder inhaler; SMI = spring-generated soft mist inhaler; NEB = nebulized' * = approved for asthma indication as well; N/A = not applicable.

disease, the long-term experience with these medications is reassuring [35].

Inhaled SABA use can exert minor effects on β1 receptors in the heart, leading to tachycardia and arrhythmias. Levalbuterol, an (R)-enantiomer of albuterol, may reduce the more cardio-specific effects from the (S)-enantiomer, with the former predominantly responsible for the bronchodilator effects. In comparison, albuterol is a racemic mixture of the (R) and (S) isomers. While levalbuterol appears to be ideal, cost and the lack of demonstrable clinical benefit have limited supplanting albuterol as the first-line SABA [36].

2.2. Anti-muscarinics

Inhaled anti-muscarinic medications such as the quaternary amines tiotropium and ipratropium achieve bronchodilation by antagonizing muscarinic receptors on bronchial smooth muscle, thereby blocking the action of acetylcholine and preventing smooth muscle contraction [23]. The cholinergic system in the lung affects smooth muscle contraction, but also inflammation in the airway epithelium and mucous secretion from goblet cells and submucosal glands [37]. Inhaled anti-muscarinics are antagonists of the muscarinic type 1 receptor (M1) and muscarinic type 3 receptor (M3), block mucous production of mucus, and result in relaxation of bronchial smooth muscles in the airway thus reversing acetylcholine-mediated bronchospasms [38]. Selectivity of blocking M3 and M1 over M2 receptors is key with M2 receptor stimulation resulting in presynaptic M2 auto-receptors that inhibit excessive acetylcholine release and increase acetylcholine mediated airway contractions. Long-acting anti-muscarinic antagonists (LAMAs) are often first-line therapy in patients with COPD. For patients with low symptom burden (GOLD group A), LAMA use may be superior to LABA therapy [39].

Data (and experience) show that the addition of short-acting anti-muscarinic (SAMA) to long-acting beta-agonists (LABA) can increase exercise capacity and improve lung function and symptoms [40]. The use of SAMA is more debatable in the context of regular LAMA use. Adding a SAMA does show benefits in lung function in this context but is generally avoided due to higher rates of anti-muscarinic side effects, especially urinary retention in men with known prostatic hypertrophy, and theoretical concern for competitive binding with the LAMA [41,42].

Like beta2-agonists, it is not clear if LAMA use is associated with increased cardiac disease, as stimulation of the M_2 receptor is associated with tachycardia [43]. Post-hoc analysis of the ASCENT-COPD trial showed no increased cardiac events in patients with known cardiac disease given LAMA and LABA [43].

In a large comparative effectiveness study, multiple combined inhalers with combinations of various LAMA and LABA agents demonstrated a reduction in exacerbation rate and pneumonia compared to salmeterol/fluticasone propionate (HR .73, 95% CI, 0.59–0.90), although there was a significant variance between other LABA/inhaled corticosteroid combinations and inhaled LAMA/LABA agents [44].

2.3. Inhaled corticosteroids

Inhaled corticosteroids (ICS), such as fluticasone and budesonide, penetrate airway epithelial cells upon inhalation and bind to intracellular glucocorticoid receptors, forming a complex that then translocates into the nucleus, leading to the transcription of myriad anti-inflammatory pathways such as interleukin-6, mitogen-activated protein kinase phosphatase-1 (MKP-1), and tumor necrosis factor-alpha. [45,46]. In COPD, ICS administered in combination with bronchodilators can up-regulate beta2 receptors, increasing the effect and preventing tachyphylaxis [47]. Complementary, the administration of beta2-agonists can increase the translocation of glucocorticosteroids into the nucleus [47]. Table 2 summarizes major ICS.

Clinically available ICS (and all corticosteroids (CS) in fact) can vary in potency, duration of action, and systemic bioavailability.

Table 2. Various inhaled corticosteroids (ICS) used in COPD. Many of these products are only approved for asthma.

Ages 12 years and older			
Medication	Low Dose	Medium Dose	High Dose
Budesonide Nebs (Pulmicort Respules)	0.25 mg BID	0.5 mg BID	1 mg BID
Beclomethasone (Qvar)	40 to 80 mcg BID	120 to 160 mcg BID	200 to 320 mcg BID
Budesonide (Pulmicort Flexhaler)	90 to 180 mcg BID	270 to 360 mcg BID	450 mcg to 720 mcg BID
Ciclesonide (Alvesco)	80 mcg BID	160 mcg BID	240 to 320 mcg BID
Fluticasone Furoate (Arnuity Ellipta)	100 mcg per day	100 mcg per day	200 mcg per day
Fluticasone Propionate (Flovent HFA)	44 to 88 mcg BID	110 to 220 mcg BID	440 to 880 mcg BID
Fluticasone Propionate (Flovent Diskus)	50 to 100 mcg BID	150 to 250 mcg BID	300 to 500 mcg BID
Fluticasone Propionate (ArmonAir Digihaler)	55 mcg BID	113 mcg BID	232 mcg BID
Mometasone (Asmanex HFA)	100 mcg BID	200 mcg BID	300 to 400 mcg BID
Mometasone (Asmanex Twisthaler)	110 to 220 mcg per day	330 to 440 mcg per day	550 to 880 mcg per day

Nebs = nebulization of drug; BID = twice-a-day; HFA = metered dose device using hydrofluoroalkane (HFA) as the propellant.

These differences can significantly impact their clinical effectiveness and safety profiles. For instance, medications such as fluticasone propionate and budesonide are considered high-potency corticosteroids, requiring lower doses to achieve therapeutic effects due to their strong affinity for glucocorticoid receptors and potent anti-inflammatory actions within the lungs [45]. Conversely, low-to-medium-potency corticosteroids like beclomethasone dipropionate and ciclesonide offer effective anti-inflammatory control but with a reduced risk of systemic side effects due to lower bioavailability and faster clearance from the body [48]. A study evaluating the differences in efficacy and safety among ICS/LABA combination found that those containing fluticasone had an odds ratio for severe pneumonia of 2.1 while those combination inhalers with budesomide were 1.17 and other ICSs in COPD were 1.41 [49]. These medications may be suitable for patients requiring maintenance therapy with a focus on minimizing systemic corticosteroid exposure, especially in individuals prone to corticosteroid-related adverse effects such as osteoporosis or adrenal suppression.

Low doses of corticosteroids are highly effective at reducing eosinophilic/type 2 inflammation. While this is traditionally associated with asthma, there is considerable concurrence of asthma in COPD and acknowledgment of type 2 inflammation in COPD [50,51]. COPD has historically been viewed as a predominantly neutrophilic disorder, which requires much higher doses of corticosteroids to modulate [51].

CS have long been an integral part of the management of COPD, due to their potent anti-inflammatory properties, but recent evidence suggests only certain groups of patients may benefit from scheduled ICS. Patients with frequent and/or severe exacerbations appear to benefit most [52]. The IMPACT trial demonstrated an approximately 25% reduction in moderate and severe exacerbations with the addition of ICS (the low-to-moderate dose of 100-µg fluticasone furoate) to LAMA/LABA therapy but with an increased HR of 1.53 for pneumonia with the inclusion of ICS [53]. In the ETHOS trial, patients received ICS at either 320 µg or 160 µg of budesonide twice per day were compared to ICS/LABA and LAMA/LABA [52]. As in IMPACT, moderate and severe exacerbations were reduced by about 25%, but with no increased risk of pneumonia in this cohort. Notably, ETHOS nor IMPACT demonstrated decreased mortality, but ETHOS has been found to have a high number of patients previously diagnosed with asthma and both suffered from the risk of ICS withdrawal [54].

Recent studies have highlighted the role of blood eosinophils as a biomarker for predicting the efficacy of inhaled corticosteroids (ICS) in patients with chronic obstructive pulmonary disease (COPD). Elevated blood eosinophil levels have been associated with a better response to ICS therapy. The FLAME study showed that patients with higher eosinophil counts (≥2% or ≥300 cells/µL) experienced a greater reduction in exacerbation rates when treated with ICS in combination with long-acting bronchodilators compared to those with lower eosinophil counts [55]. Numerous subsequent post-hoc and pooled analyses have demonstrated both an association with exacerbations and higher peripheral eosinophil levels, in addition to no efficacy of ICS in patients with eosinophils <100 cells/µL [51]. ETHOS showed no benefit of ICS with eosinophils <150 cells/µL. Post-hoc analysis of IMPACT showed benefits for those with prior moderate and severe exacerbations with eosinophils over 100 cells/µL [56]. Furthermore, a meta-analysis by Bafadhel et al [57]. confirmed that blood eosinophil levels could predict the likelihood of benefiting from ICS therapy. The 2024 GOLD guidelines recommend ICS in patients with eosinophils over 300 cells/µL and COPD without concurrent asthma or multiple prior cases of pneumonia [23].

In stable COPD, ICS are not shown to improve lung function or mortality [58]. Despite GOLD guidelines recommending against the use of ICS in this population, as many as ~40% of group B patients are receiving ICS in practice [51]. There is concern that rapid withdrawal of ICS can induce exacerbation. In a cohort of patients without frequent exacerbation, Patel et al. found no increase in exacerbation after appropriately discontinuing ICS [59]. Numerous other clinical trials found an increase in exacerbations after abrupt withdrawal of ICS in patients with prior exacerbations. The available evidence

suggests patients can be taken off of ICS without weaning regardless of the severity of lung disease, but not in those patients with a history of exacerbations [60]. While weaning protocols exist, they are uncommonly used in clinical practice [60].

However, the use of ICS in COPD is not without risk. The use of ICS, especially at higher doses, is associated with higher rates of corticosteroid local (candidiasis, dysphonia) and systemic (pneumonia, osteoporosis, glaucoma) adverse effects [61,62]. Systemic exposure of ICS is primarily determined by drug clearance and bioavailability. All of the clinically available ICS are metabolized in the liver via the CYP enzyme, therefore those with impaired liver function or other CYP modulators should be considered if high dose required. Systemic effects of ICS, though less frequent than with oral corticosteroids, can occur particularly with higher doses, prolonged use, and poor inhaler technique [18]. Even adrenal suppression can occur when ICS are used at high doses over extended periods [45]. Long-term use of ICS has also been associated with an increased risk of osteoporosis and bone fractures, particularly in elderly patients or those with other risk factors for osteoporosis [48]. Diabetes and bone fracture have been associated with high-dose ICS, but the correlation is less clear [63].

Multiple studies have shown that ICS use in patients with chronic obstructive pulmonary disease (COPD) is associated with an increased risk of pneumonia. The risk appears to be dose-dependent, with higher doses correlating with greater risk. GOLD and the Canadian Society Recommendations reference this increased risk [23,64]. A systematic review by Miravitlles et al. also found no increased risk with shorter half-life ICS such as budesonide [63].

Careful patient phenotyping selection with monitoring are essential to balance the benefits of inflammation control against the risks of adverse effects. In patients without concurrent asthma, the Global Initiative for Chronic Obstructive Lung Disease [23]. guidelines recommend using blood eosinophil counts to predict exacerbation risk and tailor ICS treatment [23]. Patients experiencing 2 or more moderate or 1 or more severe exacerbations per year with higher eosinophil counts (≥300 cells/μL) are recommended to use ICS therapy and should be considered for triple therapy (LABA + LAMA + ICS). Those without frequent exacerbations and with lower eosinophil counts (≤100 cells/μL) may not benefit as much and face an increased risk of pneumonia from ICS use, therefore ICS should be avoided.

2.4. Inhaled drug delivery

In inhaled drugs, medications are paired with a myriad of devices and approaches (Table 3). Therefore, drug delivery to the lungs is of equal importance as the choice of medications. Several key factors, including patient technique, inspiratory flow, manual dexterity, and cognitive and coordination abilities, influence the effectiveness of drug delivery via inhalers. GOLD guidelines emphasize the importance of inhaler education and reevaluation or technique on follow-up. [23]. Peak inspiratory flow (PIF) is a point-of-care measurement with increasing clinical usage measuring the inhalation speed and force needed for adequate drug delivery, especially dry powder inhalers (DPI) which require force to deaggregate and disperse the drug. Nearly 25% of patients with observably normal inhaler technique do not have the adequate PIF for their prescribed inhaler [65]. Arthritis and other causes of impaired manual dexterity impede a patient's ability to properly handle and activate the inhaler, especially devices such as the diskus [66]. Cognitive and coordination abilities are also essential as patients must understand and accurately follow the inhalation technique, which involves steps such as shaking the inhaler, positioning it correctly, and timing the inhalation with the release of the medication [67]. Factors that affect choice of inhaler in COPD are reviewed in more detail [68]. These factors, if not properly managed, can and do lead to reduced treatment efficacy. Despite guidelines and educational efforts focusing on this issue, rates of improper use and inadequate delivery remain high, with as few as 30% of patients with adequate drug delivery [69].

Nebulization is an alternative approach to inhalers for respiratory drug delivery. No coordination is required; just simple tidal breathing water-based nebulization results in drugs precipitating out in large airways. While time and effort (cleaning, storage, etc.) are considerably longer with nebulization, patients with barriers to delivery with inhalers, including manual dexterity, cognition, and inspiratory force, can obtain better delivery [70].

2.5. Environmental impact

The environmental impact of inhalers, particularly metered-dose inhalers (MDIs), is significant due to their reliance on hydrofluorocarbon (HFC) propellants. While significantly better than their predecessors, chlorofluorocarbons (CFCs) which were banned by the Montreal Protocol in 1987 due to effects on the ozone and subsequently phased as recently as 2008-HFC are potent greenhouse gases [71]. MDIs contribute to global warming, as HFCs have a high global warming potential (GWP), many folds worse compared to carbon dioxide [72]. Dry powder inhalers (DPIs) and soft mist inhalers (SMIs) offer more environmentally friendly alternatives, as they do not use HFCs and have a lower carbon footprint [73]. Additionally, the production, disposal, and recycling of inhaler devices also contribute to their environmental impact. Proper disposal and recycling programs can mitigate some of these effects, but

Table 3. Characteristics of various inhaled medication approaches.

Inhaler Device Type	Peak Inspiratory Force Required	Breath Speed	Coordination Required with Breath and Actuation	Environmental Impact
Metered Dose Inhaler (MDI)	Moderate	Slow	High (easier with spacer)	High, HFC propellent
Dry Powder Inhaler (DPI)	High	Fast	Low (breath actuated)	Low, no propellent
Soft Mist Inhaler (SMI)	Low	Slow	Moderate	Low, no propellent
Nebulizer	None*	Any	None*	Multiple disposable pieces

*= only requires normal tidal breathing.

widespread implementation remains a challenge [74]. Efforts to develop and adopt inhalers with minimal environmental impact, such as those using alternative propellants or propellant-free technologies, are essential for reducing the ecological footprint of respiratory therapies.

2.6. Cost and (in)affordability

The high inhaler cost is a significant barrier to effective asthma and COPD management for many patients. Several factors contribute to this issue. A small number of large pharmaceutical companies dominate the market for inhalers with few generic options available. Patent protections on brand-name inhalers, which can get new patents with shuffling inhaler devices and drug type and dose, further restrict the availability of cheaper generic alternatives, further exacerbating the cost burden. The complexity of the inhaler mechanisms also adds to the production costs, which are passed on to consumers. Insurance coverage and pricing policies vary widely, leaving many patients with substantial out-of-pocket expenses. While there have been recent efforts in the US to address the at-times prohibitively expensive cost of inhaled medications, the cost disparity between the US and the United Kingdom for the same inhaler remains as high as 10-fold. [75].

3. Oral corticosteroids

Oral CSs are commonly used in the management of moderate (managed outpatient) and severe (requiring hospitalization) COPD exacerbations. While many clinicians offer intravenous or intramuscular administration, no benefit has been demonstrated compared to oral administration, as oral CS are rapidly absorbed, have high bioavailability, and rapid onset of peak serum levels within ~ 1 hour [76,77]. Contrary to other indications for oral CS, dosing is not commonly weight-based. Instead, 40–60 mg prednisone for 5 days is commonly prescribed for COPD exacerbations based on data demonstrating decreased risk of intensive care unit and ventilatory support use, reduced rate of treatment failure, and improved FEV_1 and symptoms when compared to placebo (and no additional benefit but increased hyperglycemia when compared to 14 days of therapy) [23,78]. There is an increasing need identified for more personalized use of CS in COPD. The study of acute exacerbations and response (STARR2) study performed in the United Kingdom (UK) randomized standard therapy to doses targeted to blood eosinophils at the time of exacerbation. This non-inferiority trial showed no difference in the two arms but found lower cumulative oral CS dose in the blood eosinophil targeted group [79].

While there are clear benefits for systemic CS in COPD exacerbations, there is also risk with myriad adverse events that can occur acutely (hyperglycemia), sub acutely (pneumonia), or chronically (osteoporosis). Adverse events from oral CS include the risk of osteoporosis, fractures, type 2 diabetes mellitus, cardiovascular/cerebrovascular disease, and all-cause mortality, are associated with increasing cumulative dose of oral CS [80]. Even short-term bursts of oral CS are associated with an increased risk of pneumonia and mortality [81]. Prescription of oral CS should be judiciously considered, balancing the severity of the exacerbation (and potential benefit) and patient-specific risks.

4. Phosphodiesterase (PDE) inhibitors in the treatment of COPD

Phosphodiesterase (PDE) enzymes metabolize cAMP and cGMP. There are 11 families of PDE, with PDE 3 and 4 of particular interest as pharmacologic targets for COPD due to their expression in airway smooth muscle and PDE4 presence in airway epithelial and inflammatory cells [82]. Inhibition of these enzymes in the airways leads to bronchodilation, anti-inflammatory effects, improved airway clearance, and prevention of the bronchial wall remodeling that can occur in COPD. Furthermore, some of these effects are additive when PDE3/4 inhibitors are used in conjunction with other bronchodilators or glucocorticosteroids [83]. Table 4 summarizes currently available PDE inhibitors for the treatment of COPD.

4.1. Theophylline

The xanthine derivative theophylline is an oral, nonselective PDE inhibitor with a known narrow therapeutic window. It has been shown to have limited utility in the management of COPD. A randomized control trial investigating the addition of low-dose theophylline to inhaled corticosteroids in patients with COPD at high risk of exacerbation found it did not significantly reduce the rate of moderate-to-severe exacerbations over a 1-year period [84]. It did demonstrate a significant difference in the number of exacerbations treated in the hospital, most notably in a small subset of frequently hospitalized patients, but not in the number of non-COPD hospitalizations, nor episodes of pneumonia, lung function as measured by

Table 4. Current phosphodiesterase inhibitors available for the treatment of COPD.

PDE inhibitors in COPD

Medication	PDE target	Route	Benefit	Adverse Effects	Other Considerations
Theophylline	non-selective	oral	Mildly improved lung function and arterial blood gas tensions	Nausea, headaches, insomnia, dyspepsia, supraventricular arrhythmias	Narrow therapeutic window requires erum level monitoring. Many drugrug interactionss and diseaseeasestates influencence metabolism
Roflumilast	PDE 4	oral	Improve lung function, reduce rate of exacerbations	GI side effects	Narrow therapeutic index
Ensifentrine	PDE3/4	nebulized	Improve lung function, reduce rate of exacerbations, improved symptoms and quality of life	Hypertension, back pain, UTI	Recently approved by by EMA and FDA, expected to become available soon

PDE = phosphodiesterase; GI = gastrointestinal; UTI = urinary tract infections; EMA = European Medicines Agency; FDA = US Food and Drug Administration.

FEV_1, or measurements of quality of life or health status. Importantly, the use of theophylline as an adjunctive therapy was not associated with increased adverse reactions or events, or mortality [84].

A systematic review assessing the use of theophylline in stable COPD in 20 crossover, randomized controlled trials, found statistically significant improvement of lung function with an increase of 100 mL in FEV_1, ventilatory capacity, and arterial blood gas tensions [85]. Additionally, patients preferred theophylline to placebo, despite a greater association with gastrointestinal side effects. There was no significant difference in distance walked, Visual Analogue Scale (VAS) for breathlessness, symptoms of wheeze and dyspnea, or exacerbations. Notably, a majority of the included studies allowed concomitant use of other bronchodilators and inhaled corticosteroids, while some did not, and others did not specify [85].

Theophylline was associated with significantly more nausea, while other side effects include headaches, insomnia, dyspepsia, and the potential for supraventricular arrhythmias [85]. Theophylline is a challenging drug to use in practice due to many drug-interactions that influence its metabolism and require increased monitoring, notably including antibiotics such as erythromycin, clarithromycin, and quinolones, as well as disease states including heart failure, pneumonia, and viral infections [86].

4.2. Roflumilast

Roflumilast is an oral, selective PDE4 inhibitor that has been shown in large clinical trials to improve lung function and reduce rate of exacerbations in severe COPD, particularly in conjunction with long-acting bronchodilators, and in patients with a chronic bronchitis phenotype [82].

An early phase 3 trial and a large multiple-centered randomized controlled trial (RCT) (REACT) that evaluated oral roflumilast in combination LABA/ICS inhalers found moderately reduced COPD exacerbations and improvement in health-related quality of life measurements [87,88]. A year-long, phase 4 trial (RE^2SPOND) that randomized 2,354 COPD patients on LABA/ICS inhalers failed to show statistically significant reductions in moderate and/or severe COPD exacerbations [89]. A small phase 2 RCT evaluated the effect of roflumilast added to standard COPD treatments [90]. A small non-statistically significant greater increase in FEV_1 of 94 mL was seen at Day 28. The use of roflumilast compared to placebo significantly reduced the percentage of sputum neutrophils (−13.9%, 95% CI, −27.8% to −0.09%, $p = 0.018$) [90]. A systematic review of PDE4 inhibitors in the treatment of COPD included 34 separate RCTs evaluating roflumilast (20 trials with a total of 17,627 patients) and cilomilast (14 trials with a total of 6,457 patients) [91]. The mean difference in FEV_1 over the trial period was 51.53 mL with the PDE4 inhibitors compared to placebo (95% CI, 43.17 to 59.90 mL), quality of life, and reduced COPD exacerbations (OR = 0.78, 95% CI, 0.73 to 0.83) [91]. Like theophylline, roflumilast has a narrow therapeutic index, and is poorly tolerated due to gastrointestinal side effects [92].

4.3. Ensifentrine

More promising, is the advent of inhaled dual PDE3/4 inhibitors such as ensifentrine. Ensifentrine inhibits recombinant PDE3 approximately 3000-fold higher than it inhibits recombinant PDE 4 [82]. Early studies with inhaled ensifentrine found that 3 mg twice-daily was able to improve peak FEV_1 in COPD patients [93]. It also improved symptoms [94]. Improved FEV_1 was also seen when inhaled ensifentrine was added for patients on stable inhaled tiotropium [95]. Preliminary phase 2 trials suggest improved symptoms, health-related quality of life, and sustained bronchodilation [96].

The ENHANCE trials are phase III randomized control trials that demonstrated the use of nebulized ensifentrine 3 mg twice-daily in patients with moderate-to-severe COPD led to significant improvement in lung function as measured by average FEV_1 area under the curve at 0–12 hours compared with placebo, along with improved symptoms and quality of life, reduced moderate-to-severe exacerbations, and increased time to first exacerbation. Importantly, these results were consistent regardless of the accompanying use of other COPD medications, and the medication was well tolerated without increased gastrointestinal adverse effects compared with the placebo [97]. It is delivered in a standard jet nebulizer with a mouthpiece twice-a-day by putting one 3 mg ampule in the nebulizer [98]. No significant drug interactions have been reported. Recent EMA and FDA approval of this new therapy has occurred and should be available soon. The most commonly reported side effects included hypertension, back pain, and urinary tract infections [97].

5. Antibiotics in the treatment of COPD

Given the role of respiratory infections in COPD exacerbations, the use of prophylactic antibiotics has been investigated and implemented for the reduction of exacerbations. In addition to their antibiosis, macrolides in particular demonstrate benefit via their anti-inflammatory properties, including reducing airway cytokine production [99,100]. They also interfere with biofilm formation, bacterial adherence of pathogens, and have a prokinetic activity on the GI tract that may reduce reflux and micro aspiration [101]. Table 5 summarizes antibiotics commonly used prophylactically in COPD.

5.1. Erythromycin

A small, randomized control trial found that the use of erythromycin 125 mg three times daily for 6 months in patients with COPD resulted in a significant reduction of neutrophil count and activity in induced sputum, as well as in moderate-to-severe exacerbations and time to first exacerbation but did not show significant differences in health scores [99]. The addition of erythromycin 250 mg twice daily for a year in patients with moderate-to-severe COPD has also demonstrated a significant reduction in exacerbation frequency, severity, and duration, without significant difference in FEV_1 decline, nor sputum inflammatory markers or bacteriology [100]. This study monitored for known potential adverse effects, excluding patients with QTc abnormalities on cardiogram, and found no

Table 5. Antibiotics used in the prevention of COPD exacerbations.

Antibiotic	Dose	Duration	Benefit	Adverse Effects	Other Considerations
Erythromycin	125 mg TID 250 mg BID	6 months 1 year	Reduced exacerbations	GI side effects, QTc prolongation, risk of hearing impairment	Drug interactions with theophylline, benzodiazepines, cyclosporine, tacrolimus, HMG Co-A reductase inhibitors, methylprednisolone, warfarin
Azithromycin	250 mg daily 250 mg 3× weekly 500 mg 3× weekly	1 year 6 months 1 year	Reduced exacerbations		May be most beneficial in patients that are older, milder GOLD stages, not current smokers

TID = three times-a-day; BID = twice-a-day; GI = gastrointestinal; 3× = three times; GOLD = Global Initiative for Chronic Obstructive Lung Disease.

changes in QTc interval or hepatic function tests with therapy, nor a significant difference in reported gastrointestinal side effects. Additionally, due to potential interaction with theophylline, patients taking this medication had serum levels monitored, without findings above therapeutic range [100]. In addition to its interaction with theophylline, erythromycin is associated with a range of potential interactions, primarily related to CYP450, including, but not limited to, benzodiazepines, some immunosuppressants, statin therapy, methylprednisolone, and warfarin [102].

5.2. Azithromycin

Studies have shown azithromycin to be useful in reducing COPD exacerbations when added to standard therapy. A large, multicenter, randomized control trial found a hazard ratio of 0.73 (CI 0.63 to 0.84; $p < 0.001$) with the addition of azithromycin 250 mg daily for a year compared to placebo in patients with COPD at increased risk of exacerbation, as well as a prolonged time to first exacerbation (266 days in treatment group vs 174 days in placebo group, $p < 0.001$) [103]. Similarly, the COLUMBUS trial found the addition of azithromycin 500 mg three times weekly for a year in patients with COPD with at least 3 or more exacerbations in the previous year by about 40% (unadjusted relative risk (RR) 0.6, CI 0.43–0.84; $p = 0.003$). They also found treatment was associated with a significantly longer time to first exacerbation and about a 30% greater chance of remaining exacerbation-free at 6 months [104]. In a small study investigating patients with severe COPD and tracheostomy, there were two exacerbations in a group of 11 patients treated with azithromycin 500 mg daily three times weekly at 3 months, versus 12 exacerbations in 10 patients on placebo [105]. A systematic review performed by the European Respiratory Society (ERS) and American Thoracic Society (ATS) looked at four randomized control trials with varying macrolide regimens (erythromycin 200–400 mg daily, erythromycin 250 mg twice daily, azithromycin 250 mg daily, and azithromycin 500 mg 3 times weekly) for a year found a decreased rate of exacerbation (rate ratio 0.76) with a modest absolute decrease of 0.4 fewer exacerbations per patient per year, and overall recommended macrolide prophylaxis in patients with moderate-to-severe COPD and exacerbations despite optimal inhaled therapy [61].

A single-center retrospective observational study of COPD patients found that 126 patients prescribed azithromycin 250 mg at least three times weekly for 6 months had a significant decrease in the number of exacerbations (3.1 vs 2.3, $p < 0.001$) in the year after initiation, whereas 69 patients who were not prescribed antibiotic prophylaxis had significantly more exacerbations from 1 year to the next (1.7 vs 2.7, $p < 0.001$). Additionally, the treatment group continued to have significantly reduced exacerbations, Emergency Department (ED) visits, and hospital admissions beyond a year of follow-up. [101]. Interestingly, a single-center retrospective study of the COLUMBUS cohort examining patients who continued azithromycin 500 mg three times weekly after a year for the study found no significant difference in exacerbation frequency compared to participants who discontinued azithromycin after the study, [106]. suggesting there may not be benefit of continued maintenance therapy past a year, but prospective trials are needed to further investigate. The BACE trial investigated the initiation of a loading dose of azithromycin 500 mg for 3 days in patients with COPD hospitalized for acute exacerbation in addition to standard antibiotic and steroid therapy, then maintained on azithromycin 250 mg every 2 days for 3 months and followed for another 6 months. In analyzing treatment failure, defined as the composite of treatment intensification with systemic corticosteroids and/or antibiotics, step-up in hospital care, or readmission for respiratory causes, they found an 18% reduction in treatment failure within 3 months, but it did not meet statistical significance as the study was underpowered due to small sample size [107].

A Cochrane systematic review of 14 studies with varying antibiotic regimens, including nine with daily macrolides, two with intermittent azithromycin (3 times weekly), one macrolide and one quinolone pulsed (5 days every 8 weeks), and one with arms comparing continuous doxycycline, intermittent azithromycin, and pulsed moxifloxacin with placebo, found a significant reduction in the number of patients with one or more exacerbations over the treatment period (OR 0.57, CI 0.42 to 0.78; 2716 participants across 10 studies). Notably, a subgroup analysis suggested continuous and intermittent regimens may be more effective than pulsed doses. Continuous and intermittent regimens also showed a significant reduction in the rate of exacerbations per patient per year [108].

In considering which patients may benefit most from azithromycin therapy, retrospective analyses have found it may be more effective in patients who are older and have milder GOLD stages, while it may have less utility in current smokers [101,109]. Evidence also suggested treatment was better at preventing more severe exacerbations requiring intervention with both antibiotics and steroids [109].

Despite the significant reduction in exacerbations, few studies have shown clinically significant improvement in quality of life. In Albert et. al, [103]. there was a significant decrease in the St. George Respiratory Questionnaire (SGRQ), in which lower scores correspond to a higher quality of life, but it did not exceed the prespecified clinically significant difference of at least four. However, a higher proportion of patients (43%) in the treatment group did meet this difference compared with those in placebo (36%) [103]. Severe COPD patients with tracheostomy did have a significant improvement in quality of life as measured by the Maugeri Respiratory Failure questionnaire (MRF26) when treated with azithromycin [105]. The collaboration between ERS and ATS also demonstrated modest improvement in quality of life as measured by SGRQ with a mean difference less than four [61]. In the case of the COLUMBUS trial, the improvement in SGRQ was not sustained at 12 months [104].

Many studies with azithromycin excluded patients with hearing impairment, tachycardia, QTc prolongation, or risk of QTc prolongation at baseline. Some studies saw significant decrement in hearing in the treatment group, sometimes leading to premature discontinuation of therapy, although some patients had return to baseline hearing function with or without discontinuation of azithromycin [61,103]. Gastrointestinal side effects, including diarrhea and stomachache, were commonly seen with the use of antibiotic therapy [105,107]. and in some cases led to discontinuation of therapy [101]. In contrast to erythromycin, azithromycin does not appear to have many clinically significant drug interactions, probably because of its lack of complexation with CYP450 enzymes [102].

An important consideration with the use of chronic macrolide therapy is the concern for the development of antibiotic resistance. Albert et al. showed a decrease in colonization with selected respiratory pathogens, but in those who did become colonized, there was a significant increase in macrolide resistance [103]. The ERS/ATS meta-analysis found inconclusive results regarding macrolide resistance, [61]. while the BACE trial saw no significant difference in newly acquired pathogens or macrolide-resistant bacteria in sputum cultures [107].

Prophylactic macrolide therapy has shown to be effective in reducing exacerbations, leading to its use being recommended in the 2015 ACCP/CTS and 2017 ERS/ATS guidelines for patients with persistent exacerbations despite maintenance therapy [61,110]. However, both of these guidelines similarly suggest the use of roflumilast, although specifically in patients with COPD and a chronic bronchitis phenotype. No studies address the question of which medication clinicians should try first. A retrospective cohort analysis by Lam et al. used data from Veterans Health Administration (VHA) Corporate Data Warehouse (CDW) to compare outcomes in patients with COPD who were prescribed either roflumilast or azithromycin [111]. After adjusting for baseline differences, they found azithromycin was associated with slightly improved survival outcomes, while roflumilast had a higher risk of COPD-related (HR 1.21) and all-cause hospitalization (HR 1.23) [111]. The ongoing RELIANCE randomized control trial is aiming to further elucidate the comparison between these therapeutic options [110].

5.3. Moxifloxacin

The PULSE Study group performed a randomized control trial with findings that the addition of moxifloxacin 400 mg daily for 5 days every 8 weeks for 6 courses compared with placebo in stable patients with COPD reduced the odds of exacerbation by 20% in the intention to treat population ($p = 0.059$), 25% among the per protocol population ($p = 0.046$), and 45% in per protocol patients with purulent or mucopurulent sputum at baseline ($p = 0.006$). There was no significant difference in hospitalization rates, mortality, lung function, changes in SGRQ total scores, and no evidence of the development of moxifloxacin resistance. However, for patients colonized with *P. aeruginosa* at baseline, there was an increase in the median MIC for moxifloxacin, suggesting against the use of moxifloxacin in this population. There were significantly more adverse effects in the treatment group, including discontinuation of moxifloxacin due to gastrointestinal effects [112]. In addition to GI side effects, moxifloxacin, like other fluoroquinolones, comes with a risk for arrhythmia, and dysglycemia [113].

5.4. Doxycycline

A randomized, placebo-controlled trial investigating the use of doxycycline 100 mg daily for a year did not show a significant reduction in the rate of exacerbation (RR, 0.86; CI 0.67–1.10; $p = 0.23$), but a subgroup analysis did show significant reduction in patients with severe COPD (RR 0.36; CI 0.15–0.85; $p = 0.019$) and serum eosinophils less than 300 cells/μl (RR 0.50; CI 0.29–0.84; $p = 0.01$). There was no significant difference in the rate of treated exacerbations, number of hospitalizations, time to first exacerbation, FEV_1, or adverse events. However, health status as measured by SGRQ was significantly worse in the treatment group, and there were more gastrointestinal disorders seen with doxycycline, although this was not statistically significant [114]. Other considerations of doxycycline use include adverse effects including esophageal injury, bone growth inhibition, and photosensitivity, along with drug interactions with divalent cations, iron, anticonvulsants, rifampin, and warfarin [115].

6. Biologicals/monoclonal antibodies (MAB) in the treatment of COPD

The asthma-COPD overlap syndrome (ACOS or ACO) has been recognized for more than a decade now [116–119]. Type 2 (Th2) lymphocyte inflammatory-mediated airway constriction is thought to be important in asthma and in ACOS [116]. When Th2 lymphocytes are activated, dendritic cells, basophils, macrophages, mast cells and eosinophils contribute to the amplification of the pathological inflammatory pathways that include interleukins (IL) such as IL-5, IL-4 and IL-14. Monoclonal antibodies directed to components of this inflammatory cascade have been developed and approved for asthma with some tested in COPD patients (Tables 6 and 7). Most of these studies have focused on ACOS patients with evidence of Th2-mediated inflammation, such as elevated blood eosinophil counts or IgE levels. Newer agents are

looking at non-Th2 traditional mechanisms of mediated inflammation in asthma and COPD.

The treatment of cystic fibrosis has been revolutionized by drugs that work on the cystic fibrosis conductance regulator (CFTR). The CFTR is potentially damaged by cigarette smoking [135]. The acquired dysfunction of CFTR is thought to lead to airway obstruction, chronic airway inflammation and bacterial colonization by reducing airway surface liquid and decreased mucociliary transport [135,136]. Drugs that effect and improve the CFTR dysfunction associated with smoking are being evaluated in COPD patients.

6.1. Omalizumab

Omalizumab is approved for refractory asthma (Table 6). It is a humanized murine IgG MAB with binding to the CH3 domain of IgE [134]. The binding by omalizumab to IgE prevents IgE binding to mast cells, basophils, dendritic cells and monocytes reducing Th2-mediated inflammation. A large prospective, real-world study evaluating omalizumab in asthmatics called the PROSERO trial included 106 patients who met various definitions of ACOS [120,137]. They showed that omalizumab treatment in these ACOS patients decreased the rate of exacerbations and improved Asthma Control Test (ACT) scores over the 48-week trial [120]. In another study, 10 ACOS patients treated with omalizumab had a significant reduction in eosinophils and serum IL-4 levels compared to baseline levels along with improved FEV_1 and ACT scores [138]. A small study of 3 ACOS patients treated with omalizumab had improved ACT scores, reduced exacerbations, and reduced hospitalizations after 1 year compared to their baseline [139]. Maltby and colleagues [121]. reviewed the Australian Xolair Registry and identified 17 ACOS patients that had been treated with omalizumab for at least 6 months [121]. Compared to baseline, their spirometry did not improve but ACT and asthma quality of life scores improved. These relative low-quality studies without an RCT suggests that ACOS patients with elevated serum eosinophil counts may see a modest improvement with omalizumab. Further phase 3 RCTs with very defined phenotypes are needed to establish the role of omalizumab is in eosinophilic associated COPD.

6.2. Anti-IL-5/IL-5 R

As many as 20–40% of patients with COPD have ACOS manifesting as a type of eosinophilic COPD [140]. Because of their efficacy as an add-on medication in Th2-mediated asthma, anti-IL-5 and IL-5 MAB receptor antagonists have been explored in eosinophilic COPD. Two phase 3, randomized, placebo-controlled, double-blind, parallel-group trials evaluated mepolizumab in eosinophilic COPD patients. These trials were called METREX (100 mg subcutaneous (sc) mepolizumab every 4 weeks for 52 weeks) and METEREO (100 mg or 300 mg sc every 4 weeks for 52 weeks) [122]. All patients had to have at least 150 blood eosinophil cells/μL at screening or at least 300 blood eosinophil cells/μL during the previous year. The 100 mg dose of mepolizumab was found to lower the rate of COPD exacerbations compared to placebo [122]. These findings were confirmed when a meta-analysis of 1136 individual patient data from the 52-week METREX and METRED studies were combined [55]. A single-centered, retrospective, observational study of 20 elderly (age >65 years old) with COPD and at least 150 eosinophils cells per milliliter at baseline or >300 eosinophils cells/μL during the last year were treated with mepolizumab. The number of exacerbations in the previous 6 months were annualized and compared to the exacerbations 24 weeks also annualized after the mepolizumab was started. Clinically significant reductions in the COPD exacerbation rate and blood eosinophils were reported [123]. These studies suggest that patients with eosinophilic COPD or ACOS are likely to respond to the MAB mepolizumab which binds IL-5 and prevents its binding to the receptor and improves these patients [141].

Another MAB, benralizumab blocks the IL-5 receptor and has been tested in a phase 2a study of COPD patients with eosinophilia [124]. In this study, 100 mg benralizumab or placebo were randomized and given to 101 COPD patients with eosinophilia for at least 48 weeks. There was no reduction in COPD exacerbation noted in this study. Two phase 3 trials with benralizumab called GALATHEA and TERRANOVA in 2665 COPD patients with eosinophils at three different levels (>300, 220–299, and <220 cells/μL) were treated with placebo or 10, 30, or 100 mg benralizumab sc every 8 weeks were reported [125]. The primary endpoint was annualized exacerbation rates determined at week 56 in patients with eosinophil counts >220 cells/μL. The use of benralizumab was not associated with reduced exacerbation in the group with eosinophils >220 cells/μL. Two retrospective analyses have been done on the GALATHEA and TERANOVA data. When the 100 mg sc benralizumab every 8 weeks group with blood eosinophils greater than or equal to 220 cells/μL at baseline or a history of more than 3 exacerbations in the year prior were analyzed, there was a reduction in exacerbations and improved spirometry [142]. Another post-hoc analysis of these two large studies evaluated COPD patients with blood eosinophil >300 cells/μL and who had at least one exacerbation after randomization [143]. Those treated with 100 mg sc benralizumab ($N = 73$) and placebo ($N = 72$) met the above definitions and after their first exacerbation, benralizumab treatment significantly reduced further exacerbations at both 30 days and 90 days compared to placebo. Several meta-analyses, systematic reviews, and real-world retrospective studies have also suggested IL-5 MAB-directed therapy has efficacy in eosinophilic COPD phenotype [140,144,145]. Further studies such as the phase 3 RESOLUTE or ABRA trial [143]. are being done to explore if this or other COPD phenotypes will be responsive to benralizumab.

6.3. Anti-IL-4/IL-13 antagonist MABs

The fully human MAB dupilumab blocks the IL-4 and IL-13 pathways and has been approved for asthma (Table 6). Two large phase 3 trials have evaluated dupilumab in COPD patients with increased blood eosinophilia. The first trial (BOREAS) had 939 COPD patients with blood eosinophil of >300 per milliliter at screening and counts >230 cells/μL at randomization. They were treated with placebo or dupilumab 300 mg sc as an add-on therapy every 2 weeks for 52 weeks

Table 6. Monoclonal antibodies/biological therapies in COPD.

Trial name	Registration#	Author	Drug/dose	Type trial	N	Results	reference
Anti-IgE Therapy Prospero	NCT01922037	Hanania, N	Omalizumab/NR	MC, Obs Prosp, single-arm, 48-week subgroup with Asthma/COPD overlap-post hoc	737 Patients	Reduced exacerbations compared to patient baseline rate and improved asthma control test scores from the base line	[120]
NR	NR	Maltby, S	Omalizumab/NR	MC, Obs, Asthma/COPD overlap patients	17 Asthma/COPD overlap patients 160 Asthma patients	Improved HRQoL in Asthma/COPD overlap patients 3.68 to 1.69, $p \leq 0.0001$	[121]
Anti-PL-5/IL-5 R Therapy METREX/METRO	NCT02105948 NCT02105961	Pavord, ID	Mepolizumab, **METREX** 100 mg mepolizumab vs PL 48 weeks @4-week dosing **METRO** 100 mg, 300 mg, or PL for 48 weeks @4-week dosing	Phase 3, R, PC, MC, parallel-group trials	837 Asthma/COPD overlap patients with either current or history of ↑IgE	The 100 mg dose but not the 300 mg dose was associated with reduced exacerbation rates in both studies	[122]
METREX/METRO (Trial continuation results)	NCT02105948 NCT02105961	Pavord, ID	Mepolizumab 100 mg mepolizumab vs PL	Phase 3, R, PC, MC	1,136 Asthma/COPD overlap patients with current or history of IgE	Reduced rate of exacerbations RR = 0.82 (95% CI, 0.71-0.95, $p = 0.006$) Improved HRQoL	[55]
NR	NR	Isoyama	Mepolizumab NR	SC, Obs, Retro treated 24 weeks followed an additional 24 weeks	20 Asthma/COPD overlap & Asthma patients. 10 male; 10 female, mean age 77.5 ± 1.3 years with only Asthma and 11 Asthma/COPD overlap	Reduced eosinophil counts and exacerbation rates in both group, no improvement in lung function	[123]
NR	NCT01227278	Brightling	Benralizumab 100 mg every 4 weeks until week 8 then every 8 weeks through week 48 vs PL	Phase 2a, DB, PC, R	101 COPD patients with sputum eosinophils	No reduction in exacerbation rate; $p = 0.014$ improvement in pre-bronchodilator FEV_1 change from baseline to week 56 with benralizumab	[124]
GALATHEA & TERRONOVA	NCT02138916 NCT02155660	Criner, GJ	Benralizumab 30 or 100 mg every 8 weeks R, PC, (every 4 weeks first 3 doses) or 10, 30 or 100 mg in TERRONOVA vs PL total 56 weeks	Phase 3, DB, Parallel group COPD patient with frequent exacerbations matched for eosinophil count (≥220 per cubic millimeter vs < 220)	1,120 GALATHEA 1,545 TERRANOVA	No reduction in exacerbations reported	[125]
GALATHEA & TERRONOVA (Re-analysis, post hoc)	NCT02138916 NCT02155660	Criner, GJ	Benralizumab 30 or 100 mg every 8 weeks (every 4 weeks first 3 doses) vs PL total 56 weeks	Phase 3, DB, parallel group eosinophil counts ≥ 220 per cubic millimeter	3,910 total patients COPD elevated eosinophil counts	Patient treated with 100 mg benralizumab with elevated eosinophil counts and frequent exacerbations (≥3 in previous year) had ↓ exacerbations RR 0.70 (95% CI, 0.56 - 0.88). The 30 mg dose showed no reduction in exacerbations.	[126]
Anti-IL-4 and IL-13 Therapy BOREAS	NCT03930732	Bhatt, SP	Dupilumab 300 mg every 2 weeks vs PL for 52 weeks	Phase 3, MC, DB, R, PC	939 COPD patients with evidence of chronic bronchitis, absolute blood eosinophil count ≥ 300 per microliter at screening visit and at least 2 moderate or 1 severe exacerbation in last year.	Dupilumab treated patients had a reduction in moderate/severe exacerbations CRR = 0.70, (95% CI, 0.58 – 0.86, $p < 0.001$) Also improved in respiratory questionnaire and pre-bronchodilator FEV_1 at week 52.	[50]
NOTUS	NCT04456673	Bhatt, SP	Dupilumab 300 mg every 2 weeks vs PL for 52 weeks	Phase 3, MC, DB, R, PC	935 COPD patients with ↑ blood eosinophils (≥300 per microlite) at screening visit and at least 2 moderate or 1 severe exacerbations in the last year.	Dupilumab treated had reduced exacerbations (RR = 0.66 (95% CI, 0.54 – 0.82, $p < 0.001$) Improved pre-bronchodilator FEV_1 at week 52	[127]
Anti-IL-33 blocker NR	NCT03096795	Reid	Tozorakimab	Phase 1, R, DB, PC	88 mild COPD patients with single ascending doses or multiple ascending doses to Zorakimas or placebo	Drug well tolerated significant reduction in serum IL-5 and IL-13 levels compared to PL	[128]

(*Continued*)

Table 6. (Continued).

Trial name	Registration#	Author	Drug/dose	Type trial	N	Results	reference
NR	NCT03546907	Rabe, KF	Itepekimab 300 mg subcutaneous injections every 2 weeks for 24-52 weeks vs PL	Phase 2a, DB, PC, R, MC, parallel group	305 COPD patients on triple inhalers	No overall reduction in exacerbations were seen compared to placebo but when just former smokers were included, a reduction was seen RR 0.5 (95% CI, 0.39 – 0.85, $p = 0.0076$). current smokers seen no improvement in either measure	[129]
TSLP blocker COURSE	NCT0439113	Singh, D	Tezepelumab 420 mg subcutaneous injections every 4 weeks vs PL for 52 weeks	Phase 2a, DB, PC, R, MC	333 moderate to very severe COPD patients on triple inhalers	Non-statistically significant reduction in moderate-to-severe exacerbation particularly in those with elevated blood eosinophils	[130]

SC = single-center; MC = multicenter; TSLP = thymic stromal lymphopoietin; IL = interleukin; OBS = observational; Prosp = prospective; COPD = chronic obstructive pulmonary disease; HRQoL = health related quality of life; NR = not reported; PC = placebo-controlled; IgE = immunoglobin E; *R* = randomized; RR = rate ratio; CI = confidence interval; Retro = retrospective trial; DB = double blind; FEV1 = forced expiratory volume in 1 second.

[50]. Significant reduction in exacerbations and improved quality of life were found with those treated with dupilumab. A recent pre-publication of the NOTUS Trial has been released [50]. In this trial, 935 COPD patients with screening blood eosinophil count >300 cells/μL were randomized to placebo or dupilumab 300 mg sc every 2 weeks for 52 weeks. The rate of annualized moderate-to-severe exacerbations was significantly reduced with dupilumab (RR = 0.66 (95% CI, 0.54–0.82, $p = 0.001$)). A significant increase in FEV_1 was noted in the dupilumab group at weeks 12 and 52 [127]. In this COPD phenotype, dupilumab appears to be efficacious with no major adverse events.

6.4. TSLP blocker

Tezepelumab is a IgG21 and a MAB that blocks the activity of the epithelial cytokine thymic stromal lymphopoietin (TSLP). It is approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in the treatment of asthma [146]. A recent phase 2a trial in 333 patients with moderate to very severe COPD treated with placebo or 420 mg Tezepelumab subcutaneously every 4 weeks for up to 52 weeks [130]. Those patients with COPD and baseline blood eosinophils >150 cells/μL given tezepelumab had a significant 37% reduction in exacerbations compared to placebo. Further phase 3 trials to better understand the potential efficacy of tezepelumab in eosinophilia associated COPD are needed.

6.5. Anti – IL – 33

In addition to mitigating IL-5, IL-4, IL-13 and TSLP, MABs that block IL-33 have been proposed to treat Th2-mediated COPD in a step toward precision medicine [147]. Tozorakimab (MED13506) is a potent human MAB that inhibits both reduced and oxidized IL-33 through action on serum-stimulated 2 (ST2) and the receptor for advanced glycation end products/epidermal growth factor receptor (RAGE/E6FR complex) signaling pathways [148]. A phase 1, first-in-human, randomized, double-blind study evaluated safety, tolerability, immunogenicity, pharmacokinetics and pharmacodynamics of sc and intravenous doses in 56 healthy participants with a history of mild atopy getting a single escalating dose of tozorakimab [128]. A second part of the study included 24 patients with mild COPD who received multiple ascending doses of subcutaneous tozorakimab or placebo. Tozorakimab was well tolerated and demonstrated engagement with serum and nasal endogenous IL-33. The mean serum half-life was 11.7–17.3 days. It significantly reduced IL-5 and IL-13 serum levels in patients with COPD compared to placebo and was well tolerated [128].

Itepekimab is another human IgG4 MAB that is an anti-IL-33 agent. A phase 2a trial evaluated Itepekimab 300 mg given as two sc injections every 2 weeks for 24–52 weeks compared to placebo in 343 current or former smokers diagnosed with COPD in the last year [129]. A numerical but not statistically significant reduction in the annualized rates of exacerbation was seen with itepekimab (RR = 0.81 (95% CI 0.61–1.07, $p =$ 0.13)). In a subgroup analysis of former smokers with COPD,

Table 7. FDA- and ema-approved monoclonal antibodies (MAB) used in the treatment of asthma.

Name	Brand Name	MOA	T 1/2 (days)[1]	Route	Dose[3]
Omalizumab	Xolair®	Recombinant DNA derived humanized IgG 1/Kappa MAB selectively binds human IgE	26	sc	0.5 mg/kg or 75 – 375 mg sc every 2 to 4 weeks
Mepolizumab	Nucala®	Humanized IgG 1/kappa class MAB targeting IL-5 and this prevents IL-5 from binding to its receptor	11-26	sc	100 - 250 mg with usual dose 100 mg sc every 4 weeks
Benralizumab	Fasenra®	Humanized IgG 1/kappa class MAB binds to the D1 domain of IL-5 receptor alpha	7-16	sc IV	25 - 200 mg or 0.03 - 0 3 mg/kg Usual dose 30 mg sc every 4 weeks first 3 doses then every 8 weeks
Reslizumab	Cinqair® Cinqaero®#	Humanized IgG 4/kappa class MAB binds to IL-5 preventing receptor binding	~24	IV	3.0 mg/kg IV usual dose every 4 weeks
Dupilumab	Dupixent®	Full humanized IgG 4 subclass MAB that binds to IL-4 receptor alpha subunit, inhibits both IL-4 and IL-13 signaling	3-7	sc	75 - 600 mg Usual dose 600 mg sc then 300 mg every other week
Tezepelumab	Tezspire®	Human IgG 2 lambda subclass MAB binds to thymic stromal lymphopoietin (TSLP) inhibits TSLP from binding to the TSLP/IL-7 R alpha heterodimeric receptor	25.7[2]	sc	210 mg sc Usual dose every 4 weeks

EMA = European Medicines Agency; FDA = US Food and Drug Administration; MAB = monoclonal antibody; IgG = immunoglobulin G; IgE = immunoglobulin E; TSLP = thymic stromal lymphopoietin; IL = interleukin; T1/2 = terminal half-life; sc = subcutaneous; IV = intravenous; # = EMA approved name; MOA = mechanism of action; T 1/2 = terminal half-life of MAB.
1 Data from [131,132]; 2 Data from [133]; 3 Data from [134].

the reduction in COPD exacerbations reached statistical significance (RR = 0.58 (CI 95%, 0.39–0,85, $p = 0.0061$)). No changes in FEV_1 or adverse events was noted. Two phase 3 randomized controlled trials in former smokers with moderate-to-severe COPD with chronic bronchitis and >1 moderate-to-severe exacerbations in the last year (AERIFY-1/2) comparing itepekimab 300 mg sc every 2 weeks to placebo are ongoing with completion dates estimated to be around October 2025 [149]. Although promising, the role of IL-33 MAB therapy in COPD remains to be defined but the ongoing phase 3 itepekimab trials may help answer the question.

6.6. Active monoclonal antibodies and current COPD trials

A search of clinical trials.gov for monoclonal antibody treatments and COPD found registered trials for benralizumab and mepolizumab. The monoclonal antibody CM310, a humanized anti-IL-4 and IL-13 antibody is also being studied in COPD patients. A small safety and pharmacokinetic study of andecaliximab has finished in COPD subjects. Andecaliximab is a monoclonal antibody that inhibits metalloproteinase 9 that in turn, inhibits remodeling and tumor growth. A large study of 343 COPD subjects received SAR440340 (REGN3500) or placebo. SAR440340 is an IL-33 directed antibody that is also being evaluated for asthma. Subjects with bronchitis and COPD have had the safety and efficacy tested using the fully human anti-IL-8 monoclonal antibody. It is likely that many new monoclonal antibodies focused toward inflammation will be tested.

6.7. Cystic fibrosis transmembrane regulator potentiators

An acquired dysfunction in the cystic fibrosis transmembrane conductance regulator (CFTR) induced from smoking, inflammation, and infection in some COPD patients has been reported [136]. The dysfunction of the CFTR is about 50% in COPD and chronic bronchitis patients compared to that found in cystic fibrosis patients [136]. As a result of this CFTR dysfunction, CFTR potentiators used in the treatment of cystic fibrosis have been suggested as a treatment for COPD patients, particularly those with chronic bronchitis. A phase 2, multicenter, double-blind, randomized, placebo-controlled trial in moderate-to-severe COPD patients evaluated the CFTR potentiator icenticaftor as a proof-of-concept trial [135]. A total of 92 COPD patients were randomized (2:1) to icenticaftor 300 mg or placebo twice-a-day for 29 days with additional 4 weeks in which all subjects received placebo twice-a-day [135]. No change in lung clearance index was found with the CFTR potentiator but a mean increase of 50 mL in pre-bronchodilator FEV_1 and a mean increase of 63 mL after bronchodilator was seen when icenticaftor was used compared to placebo. Large phase 3 trials with increased phenotypical specificity are needed to define the potential role of CFTR potentiators in the treatment of COPD.

7. Mucolytics

A number of mucolytics have been used in the treatment of COPD and its phenotypes. Excess sputum production and chronic bronchitis are common in COPD and during COPD exacerbations. A recent study of 4,363 COPD subjects followed for a median of 9.5 years found that mortality was increased as a function of lung segments with mucous plugs on chest CT scan [150]. N-acetylcysteine (NAC), ambroxol, erdosteine, bromhexine, high molecular weight hyaluronan, and hypertonic saline have been used in treating COPD patients [151]. Routes of dosing have included intravenous (IV), oral or nebulized depending on the agent and the study. A Cochrane systematic review found with moderate confidence, that NAC, carbocysteine, and erdosteine were associated with reduction in disability days [152]. In addition, the meta-analysis of 28

studies including 6,723 patients found that treatment with mucolytics may be more likely to be exacerbation-free (OR = 1.73, 95% CI 1.56–1.91) but with only moderate-certainty. [152].

A pairwise network meta-analyses of 2,753 COPD patients in 7 RTCs that included oral dosing of erdosteine (600 mg/day), carbocysteine (1500 mg/day), and NAC (1200 mg/day) found that these mucolytics with antioxidant properties reduced the risk of acute exacerbations of COPD (AECOPD) (RR = 0.74, 95% CI 0.68–0.80) [153]. In this study, erdosteine was most effective, followed by carbocysteine, and then NAC. The study further noted that only erdosteine significantly reduced the risk of experiencing at least one AECOPD ($p <$ 0.01) and the chance of AECOP hospitalization ($p < 0.05$). A meta-analysis of 24 RCTs with 2,192 COPD patients that included studies with NAC, ambroxol, erdosteine, bromhexine, hypertonic saline and high molecular weight hyaluronan was performed [151]. Increased treatment success (RR = 1.37, 95% CI 1.08–1.73), symptom improvement (standardized mean difference (SMD) = 0.86, 95% CI 0.63–1.09), and reduced cough at follow-up (RR = 1.93, 95% CI 1.15–3.23) was seen.

7.1. Erdosteine

Erdosteine, (*N*-(carboxymethylthioacetyl)-homocysteine thiolactone) is approved by the EMA but not the FDA originally as a mucolytic and more recently, for the treatment of mercury toxicities [154]. The thiol groups are thought to be the active sites after metabolism. It is thought, in addition to being mucolytic, to have antioxidant, anti-inflammatory and antibacterial effects [154].

The RESTORE trial evaluated erdosteine 300 mg orally, twice-a-day in a randomized, double-blind, placebo-controlled trial in 467 COPD patients over 12 months with AECOPD as the primary endpoint [155]. A reduction in AECOPD events of 19.4% was seen going from 1.13 AEOPD per year to 0.91 AECOPD event per year ($p = 0.01$). The effect was primarily because of the drug's effect on mild rather than moderate-to-severe AECOPD. The duration of AECOPD events was significantly reduced with erdosteine treatment by 24.6% across the spectrum of mild-to-severe exacerbations (9.55 versus 12.63 days, $p = 0.023$) [155]. Two RCT's have demonstrated erdosteine' s ability to reduce oxidative stress in COPD patients including during exercise [156,157]. Post hoc analyses of the RESTORE trial confirmed that adding erdosteine to usual COPD maintenance treatment also reduces the number of mild AECOPD, their duration, and the number of episodes requiring antibiotics [158,159].

7.2. N-acetylcysteine (NAC)

NAC is a glutathione replacement used IV and orally in the treatment of acetaminophen overdoses to protect the liver and other organs. It can also be nebulized to thin mucous or used with direct infusion by bronchoscope to break up mucous plugs. In addition to this mucolytic effect, NAC is an antioxidant drug. It is a 'direct' scavenger of reactive oxygen species and an indirect antioxidant by providing cysteine which is a critical precursor in the synthesis of intracellular glutathione [160].

The Chinese trial PANTHEON included 1,006 COPD patients that were randomized to NAC 600 mg orally twice-a-day or placebo. PANTHEON was a randomized, double-blind, placebo-controlled, parallel-group study [160]. The year-long trial reported that the AECOPD rate was 1.16 AECOPD per patients-year in the NAC treated group and 1.49 AECOPD per patients-year in the placebo group (RR = 0.78, 95% CI 0.67–0.90, $p = 0.011$). NAC was also found to be well tolerated [160].

A single-center, retrospective cohort study in 453 COPD patients who had an AECOPD requiring hospitalization were assigned to an inhaled NAC group or a non-NAC group. A total of 192 of these patients were propensity matched. A composite endpoint of in-hospital mortality, need for mechanical ventilation, and readmission for COPD within 30 days was used. The primary combined endpoint was found to be 5.2% for the NAC treated group compared to 16.7% for the propensity matched control ($p = 0.011$) [161].

Another small single center, randomized, double-blind prospective trial in 120 COPD patients compared treatment for 6 months with NAC 600 mg orally-a-day with propolis (shown to increase tissue regeneration, anti-inflammation, antioxidant, and having some antimicrobial effects), 600 mg NAC twice-a-day with propolis, or placebo [162]. The NAC 600 mg/day with propolis treated groups showed variable improvement in symptoms and the NAC 1200 mg/day with propolis showed significantly less exacerbations compared to placebo. Another study evaluated NAC 600 mg/day plus 80 mg propolis, NAC 1200 mg/day plus 160 mg propolis or placebo in COPD patients with frequent exacerbations. This small study of 46 patients for 12 months found that the AECOPD incidence rate was 52.6% in those treated with placebo, 15.4% in those patients treated with NAC 600 mg/day plus 80 mg propolis/day, and 7.1% in the highest dosed group (1200 mg NAC/160 mg propolis/day, ($p = 0.013$) [163].

The BRONCUS trial randomized 523 COPD patients to 600 mg NAC orally daily or placebo. The patients were followed for 3 years. The primary outcomes were change in FEV_1 and rates of COPD exacerbations [164]. This study reported no difference in the FEV_1, decline or in the number of COPD exacerbations per year between the NAC treated and placebo treated groups. A subgroup analysis of COPD patients not taking inhaled corticosteroids suggested that those taking NAC had fewer COPD exacerbations (0.96 per year versus 1.29 per year, Hazard Ratio (HR) = 0.79, 95% CI 0.631–0.989, $p = 0.04$) [164].

Several meta-analyses and systematic reviews have focused on NAC therapy in COPD patients. A report using 12 trials, and 2,691 COPD patients found that both high-dose and low-dose NAC reduced exacerbations when given >6 months but not when given short-term NAC [165]. No effect on FEV_1, FVC, or inspiratory capacity was seen with NAC. Another systematic review and meta-analysis of 15 studies published in English found improvement in FEV_1 and FEV_1 /FVC with NAC treatment [166]. In addition to the spirometry improvement, COPD-related symptoms improved. An additional meta-analysis in nine RCTs with 1,076 COPD patients was used in this study. No significant change or difference in symptoms, pulmonary function decay,

number or rate of exacerbations was seen [167]. A recent meta-analysis of trials using NAC treatment in COPD and chronic bronchitis patients used 20 studies. The incidence of exacerbations as compared to placebo decreased (incidence rate ratio (IRR) = 0.76, 05% CI 0.59–0.99). NAC treatments greater than 5 months confirmed these results [168]. Variable results in meta-analyses suggest significant study design and patient phenotype differences. A reduction in COPD exacerbations seems to be consistently reported with oral NAC when used longer than 5–6 months but reductions in spirometry declines are not as consistently found with oral NAC treatment in COPD patients.

8. Expert opinion

The understanding of the complex syndrome of COPD and its various endotypes and phenotypes continues to expand. With this expansion, new pharmacological therapeutic options emerge, and old options become more precisely applied. Routine inhalers both short- and long-acting anti-muscarinics and beta2-agonists delivered by dry powder, metered doses, spring driven mist inhalers to nebulizer-based medications are key treatments. Single-device combination inhaler therapies, including SABA/SAMA, LAMA/LABA, LABA/ICS, and LAMA/LABA/ICS, are available and have reduced the burden of dosing frequency and difficulty for patients leading to improved compliance. The use of MAB therapy, particularly dupilumab, is an exciting option to curb exacerbation frequency and slow lung decline in patients Th2 inflammation. Improved agents targeting known pathway such as the recently FDA-approved inhaled PDE 3/4 inhibitor ensifentrine have arisen demonstrating benefit with fewer off-target effects.

Despite the hope gained by the new medications available, there is considerable work to be done to improve how care is delivered to patients with COPD. Barriers include immediacy bias (treating exacerbations without an eye on future suppression), high cost (unaffordable inhaled medications), access to care, and perhaps most difficult to address, a history of nihilism that has shrouded COPD care and patients. The use of azithromycin stands testament to the lack of medications not being the entire problem. For over a decade, there has been considerable evidence from multiple randomized clinical trials demonstrating benefit from azithromycin in suppressing COPD exacerbation frequency by 20–30%, yet very few patients who meet criteria actually get prescribed this affordable and well-tolerated drug [101,103–109].

With more to offer select groups patients with COPD, clinicians and health systems need to change their approach. With more nuances of care and specialty needs (e.g. respiratory therapist assessment of adequate drug delivery and technique, MAB education and administration), it is likely there will be a rise in COPD-focused clinics. For all clinicians, there will need to adapt to this rapidly changing field by educating themselves on identifying the treatable phenotypes and endotypes of disease. Clinics and clinicians are only a piece: institutions will need to develop approaches to manage COPD patients at every touch point in the system (clinic, hospital, emergency department, lab, etc.) and support the infrastructure needed for the aforementioned targeted care.

The pharmacotherapeutics for the COPD patient have evolved dramatically in the last 20 years. We anticipate even more new therapeutic potions to come in the next 20 years, hopefully with the necessary clinical reorientation on how COPD is managed. As enthusiasm for more effective medicines spur the field toward personalized medicine, our hope is that equal effort is paid to screening, prevention (smoking cessation), social determinants of health, and access to care so this benefit both equitably and cost-effectively improves the care of COPD patients.

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B T Kuhn declares he has been on the speaker bureau for Takeda and Grifols. He also is on an advisory board for GSK and Verona. The other authors have nothing to declare. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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