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Pharmaceutical Approaches In The Management Of Chronic Obstructive Pulmonary Disease (Copd): A Review Of Current And Emerging Therapies

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Abstract

Chronic obstructive pulmonary disease is a progressive respiratory condition characterized by persistent airflow limitation and systemic complications, contributing significantly to global morbidity and mortality. The symptoms should be managed with proper pharmaceutical management and even prevent exacerbations and improve the quality of life. This review has provided a comprehensive overview of the current and new pharmacological management, such as bronchodilators, inhaled corticosteroids, and combinations. It also looks at the application of biologic agents, kinase inhibitors, and new anti-inflammatory mediators in blocking the disease-specific pathways. The regenerative strategies, such as mesenchymal stem cells and gene-based treatments, as a prospective treatment option, are also mentioned. Among the priorities is the transition of the paradigm to personalized care based on the phenotypic and endotypic characterization, biomarkers, and pharmacogenomics to enable targeted interventions. However, there are still certain problems, such as compliance, inhaler compliance, polypharmacy, and access to affordable treatment. The review talks about these obstacles and the need to come up with real-life evidence and long-term safety. Moreover, the combination of digital inhaler technologies and intelligent monitoring systems is mentioned as a way to maximize adherence to treatment and monitor the disease. Finally, the article highlights the need to carry on research, innovation, and clinical translation to reach effective, individualized, and sustainable pharmaceutical care as a management approach to chronic pulmonary disease.

Keywords: *chronic pulmonary disease, pharmacological therapy, precision medicine, stem cell therapy, drug development, treatment challenges*

1. INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a progressive and irreversible pulmonary disorder that is typified by persistent airflow limitation, which is usually accompanied by defective inflammatory response to hazardous particles or gases in the lungs. There are two predominant clinical phenotypes of the disease: chronic bronchitis, where there is persistent cough and mucus hypersecretion, and emphysema, where there is destruction of alveolar walls and loss of elasticity of the lungs. Although these conditions tend to overlap, the combination of the two enhances the heterogeneous nature of COPD. The most recent clinical categories in the GOLD 2023 report are symptom- and risk-based, and they include severity indices, which include symptom burden, frequency of exacerbations, and airflow limitation as tested by spirometry (Adrianison et al., 2024). This kind of multidimensional system enables a more individual stratification and management of patients.

The impact of COPD has increased tremendously in the last thirty years, and it is still among the top causes of mortality and morbidity in the world. Soriano et al. (2020) in their global analysis of 1990-2017, noted that more than 300 million people are living with chronic respiratory diseases, with COPD being the primary cause of morbidity and mortality. The study highlighted that there is a significant rise in prevalence, especially in low and

middle-income countries, where diagnostic facilities and access to treatment are still not very high. This growth is further compounded by the fact that the populations are ageing, urbanization, and exposed to risk factors such as smoking and air pollution. Consistent with these data, Lozano et al. (2012) found that COPD was one of the five leading causes of death in the world in 1990 and in 2010 and that it had not reduced significantly in the number of deaths attributed to the condition despite the improvement in clinical knowledge and treatment strategies. This ongoing menace to the health of the people highlights the importance of effective prevention and management strategies that will target clinical as well as structural factors of the disease. The burden of COPD is also socioeconomic because the disease is chronic and progressive, hence leading to a high number of healthcare visits as well as productivity loss.

COPD is multifactorial, and the most frequent and avoidable cause is smoking tobacco. The combination of socioeconomic status and exposure risks, however, shows that they play a significant role in determining the prevalence of disease (Burney et al., 2014). The results of their study, the BOLD study, highlighted the huge disparity faced by the people in the poorer regions where there is a high prevalence of environmental pollutants and the use of biomass fuels. Besides, there are work-related exposures to dust, chemicals, and fumes, which are also significant factors, particularly in the industrial environment where there is no proper regulation. Notably, smoking is not the only factor that contributes to the development of the disease. A significant percentage of COPD cases are present in non-smokers, as described by Salvi and Barnes (2009). Their research showed that indoor air pollution, especially that caused by using biomass to cook and heat our houses, is a main factor in the development of illness among women in the rural parts of developing countries. In addition, genetic susceptibilities such as alpha-1 antitrypsin deficiency compound the issue of disease pathogenesis. Such findings contradict the conventional wisdom that COPD is a smoker's disease and that more environmental and population health prevention is needed. In the past few years, there have been great improvements in knowledge regarding the pathophysiology of COPD. According to Agustí and Hogg (2019), the maintenance of the destruction of lung tissue depends on chronic inflammation, the imbalance between proteases and antiproteases, and oxidative stress. The cellular architecture of COPD entails the neutrophilic inflammation, macrophage activation, and CD8+ T- T-lymphocyte-mediated destruction that leads to the structural changes of the airways and the destruction of the alveoli. This molecular knowledge has offered new possibilities in the form of particular pharmacological treatments that are no longer symptomatic but that alter the disease process.

Pharmacotherapy forms the foundation of the COPD treatment. It is effective in the treatment of symptoms, improvement of the quality of life, reduction in the frequency of exacerbations, and delay in the disease progression. In the current COPD management, monotherapy has been replaced by a more sophisticated approach of using long-acting bronchodilators, inhaled corticosteroids, and combinations depending on the patient phenotype and exacerbation history (Singh et al., 2019). Triple inhaler therapy and fixed-dose combinations have enhanced treatment compliance and clinical outcomes in most populations. Nevertheless, as the proportion of treatment-resistant cases has increased and it has become apparent that the disease is heterogeneous, there has been a shift towards considering new possibilities such as biologics, phosphodiesterase inhibitors, and regenerative therapies. It can be that exacerbations in COPD are not overemphasised. These acute worsening events are associated with faster decline in lung function, more health care use, and deaths. Wedzicha et al. (2013) have identified the so-called phenotype of frequent exacerbators with an increased level of inflammation and more aggressive treatment. This supports the need to individualize treatment based not only on the severity of the symptoms but also on the risk of exacerbation, thus increasing the precision of treatment.

Regardless of these developments, there is still an urgent requirement for modern synthesis and publication of evolving pharmaceutical approaches in the management of COPD. Even though bronchodilation and the management of the inflammatory process remain the most important pillars of the therapeutic process, the appearance of drug delivery, pharmacogenetics, and biomarker-based treatment is significantly changing the sphere at an impressive pace. To incorporate these innovations into everyday practice, one needs to have an in-depth knowledge of the existing and new treatment modalities.

The objectives of this review are twofold:

1. To give a current and organized description of the presently used pharmaceutical treatments in the management of COPD with emphasis on their mechanisms, efficacy, and clinical application.
2. To identify and critically evaluate new pharmacological methods that are being studied to determine how they can be incorporated into the future management system of COPD.

2. METHODOLOGY

The given narrative review was conducted by searching and analyzing the current literature related to COPD pharmacotherapy in the largest scientific databases. The selection of studies was done on the basis of the emphasis in terms of pharmaceutical interventions, both on the existing standard treatments and on the new drugs. The clinical guidelines and the randomized trials as well and the systematic reviews were given priority. Only sources written in English were taken into account. The identified data were organized by theme so as to have a clear picture of the therapeutic approaches to the management of COPD.

The steps of the methodological process adopted in this review are presented in Figure 1, where the steps involved in identifying the literature, screening, inclusion/exclusion criteria, thematic classification, and data extraction and synthesis are presented in a step-by-step manner. This method was adopted to ensure consistency and precision in the selection and examination of the most relevant research.

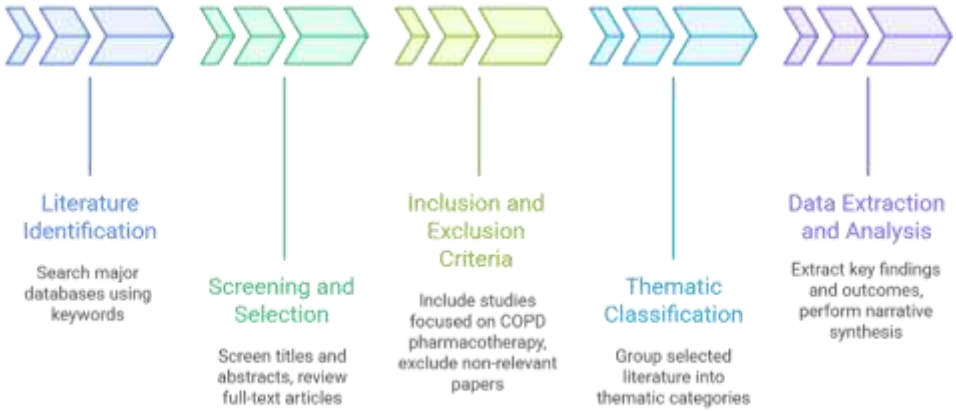

Figure 1. Stepwise Methodological Framework for Literature Review and Data Synthesis

3. Pathophysiology and Therapeutic Targets in COPD

Chronic Obstructive Pulmonary Disease (COPD) is a multifactorial and progressive lung disease that is defined as the limitation of airflow that is persistent because of a complex interaction of the inflammatory, oxidative, proteolytic and structural processes. At the center of its pathology lies the chronic airway and lung parenchymal inflammation that continues to occur long after the inciting agent, which may be tobacco smoke or environmental pollution, is no longer present. As stressed by Barnes (2016), this inflammation is essentially both innate, as well as adaptive, and macrophages, neutrophils, and CD8+ T-lymphocytes are more significant in tissue destruction and reconstruction in this case. The continued inflammatory cell infiltration also plays a major role in thickening of the airways walls, hypersecretion of mucus, fibrosis, and destruction of alveoli. According to Liu et al. (2017), it is particularly neutrophils that are extremely abundant in the sputum and bronchoalveolar lavage fluid of patients with COPD, and in case of excessive activation, they release serine proteases, myeloperoxidases, and neutrophil extracellular traps (NETs), which destroy epithelial cells and prevent mucociliary clearance. In the same line, the alveolar macrophages release pro-inflammatory mediators (TNF-alpha and IL-8) which add to the neutrophilic inflammation and initiate the matrix metalloproteinases (MMP) which destroy the connective tissue architecture.

Another more devastating role in this process is played by oxidative stress and imbalance of the proteases antiproteases. The oxidative stress caused by reactive oxygen species (ROS) in cigarette smoke and inflammatory cell activity not only harms epithelial and endothelial cells but also enhances the inflammatory process through redox-sensitive transcription factors such as NF-kappaB and p38 MAPK as proved by Addissouky et al. (2024). It is this cancerous loop that leads to the development of emphysema and bronchial obstruction. Besides, the destruction of antiproteases, including α-1 antitrypsin by ROS makes the lung extremely vulnerable to proteolytic injury. Although Oriano et al. (2021) study bronchiectasis, their results on the protease-antiprotease imbalance, especially neutrophil elastase and MMPs, are also relevant in COPD, as it is seen in the overlap in the mechanism of the two diseases. The relationship between the causes of COPD and inflammation, the response of immune cells, oxidative stress, and imbalance of proteases is graphically illustrated in Figure 2 below in a holistic manner.

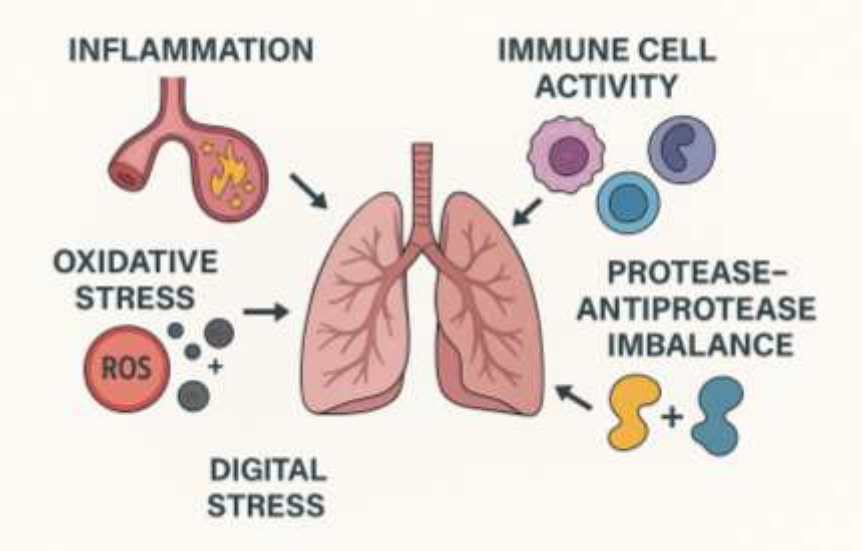

Figure 2. Mechanistic Pathways in COPD Pathogenesis

Schematic diagram of the interaction of neutrophils, macrophages, CD8+ T-cells, oxidative stress and protease-antiprotease imbalance to cause the development of airway remodeling and destruction of the lung. It is based on these mechanisms on a basic level that a therapeutic target is found. Khaliq et al. (2012) stated that the present-day pharmacological approach is focused not only on symptomatic treatment but also on acting on the mechanisms of the disease, including inhibiting phosphodiesterase-4 to suppress cytokines of inflammatory origin, using antioxidants such as N-acetylcysteine to neutralize ROS, and using protease inhibitors to restore the balance of proteolysis. To intervene, the patient should be understood in terms of clinical phenotype since not every patient has the same pathophysiological drivers.

Phenotyping has been necessitated in the personalization of treatment. Ricciardolo et al. (2023) reviewed the comorbidity of asthma and COPD, especially in the so-called asthmaCOPD overlap (ACO) phenotype that is characterized by eosinophilic inflammation and is more responsive to corticosteroids. Comparatively, the classical form that is emphysema-predominant is likely to be neutrophilic inflammatory and also more likely to respond to bronchodilator and anti-protease treatment. Bonato (2023) also pointed out the necessity to identify common and unique inflammatory profiles in asthma and COPD to facilitate the better match of treatment with the biological pathways.

The technologies of phenotype imaging have also perfected phenotype identification. Sanders et al. (2018) demonstrated that high-resolution computed tomography (HRCT) and quantitative imaging could distinguish between emphysematous and airway-predominant disease and track the evolution of the disease, and determine its reaction to treatment. Such imaging phenotypes are associated with different inflammatory and structural features, which can be used to conduct precision medicine in COPD. To make the process of stratification easier, Table 1 shows the most important COPD phenotypes, their inflammatory phenotypes, and pharmacologic targets.

Table 1. COPD Phenotypes, Inflammatory Characteristics, and Targeted Therapies (Han et al., 2010)

Phenotype	Dominant Inflammation	Pathophysiologic Features	Targeted Therapy
Emphysema-dominant	Neutrophilic	Alveolar wall destruction, hyperinflation	Bronchodilators, protease inhibitors
Chronic bronchitis	Neutrophilic + mucus hypersecretion	Goblet cell metaplasia, airway narrowing	Antimuscarinics, macrolides
Frequent exacerbator	Mixed (neutrophilic/eosinophilic)	Recurrent inflammation, lung function decline	ICS, PDE-4 inhibitors, long-acting bronchodilators
ACO (Asthma-COPD overlap)	Eosinophilic	Airway hyperreactivity, reversibility	Inhaled corticosteroids, anti-IL-5 biologics

Overall, the pathophysiology of COPD is very complex, and a combination of immune cell-mediated inflammation, oxidative and proteolytic damage, and phenotypic heterogeneity is involved. The insights that have been acquired by the understanding of such processes have not only facilitated the understanding of the disease processes but also enabled the development of more specific and mechanism-based treatment strategies. The current studies on biomarkers, imaging, and immunological signatures will enhance personalized care of COPD management further.

4. Current Pharmacological Therapies

The pharmacological treatment of Chronic Obstructive Pulmonary Disease (COPD) has been changing considerably with the change in classes of therapeutics and a better comprehension of the morbidity of the disease as well as its phenotyping. Pharmacological treatment is used to relieve the symptoms, decrease the number and severity of exacerbations, enhance health status, and improve exercise tolerance. The major groups are bronchodilators, inhaled corticosteroids (ICS), combination products, and adjunctive medications that are phosphodiesterase inhibitors, theophylline, mucolytics, and long-term antibiotics.

4.1 Bronchodilators (LABAs, LAMAs, SABAs, SAMAs)

All severities of COPD are treated with bronchodilators as a first-line treatment. Maintenance therapy should be with long-acting beta-2 agonists (LABAs) or long-acting muscarinic antagonists (LAMAs) since they have a long-acting effect, but short-acting agents (SABAs and SAMAs) should be used in severe cases or when rapid relief of symptoms is needed.

Koarai et al. (2020) have done a systematic review and meta-analysis of LABA and LAMA monotherapies in stable COPD. Their data demonstrated that the LAMAs were much more effective in lowering exacerbations and increasing trough FEV1, and therefore, are a monotherapy of choice in most clinical guidelines. Combination bronchodilation has gained prominence in recent clinical practice. In comparison with the monotherapies, LABA + LAMA has greater impacts on the lung functions and symptom control. Cazzola et al. (2022) state that the bench-to-bedside experience of dual bronchodilation has been successful with an enhanced exercise performance and patient outcome reports.

Miravitlles et al. (2022) emphasized that the majority of international recommendations, including GOLD, had started to recommend LABA/LAMA as a first-line treatment of symptomatic patients at low risk of exacerbations, as its benefit-to-risk profile is favorable. The mechanism of action and clinical stratification used to make decisions on bronchodilator therapy are presented in Figure 3 below.

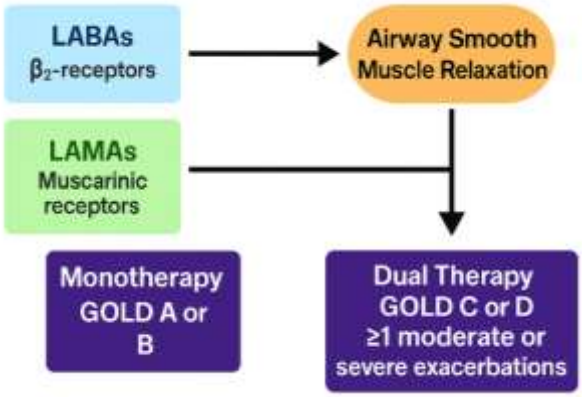

Figure 3. Mechanisms and Clinical Stratification for Bronchodilator Use in COPD

The flowchart of the effects of LABAs and LAMAs on the relaxation of airway smooth muscle and the suggestions of either monotherapy or dual therapy according to the GOLD classification and the history of exacerbation is also offered. Rodrigo et al. (2017) used meta-analysis to come up with the conclusion that LABA/LAMA combinations were better in terms of lung function and exacerbation rates as compared to LAMA monotherapy or LABA/ICS.

4.2 Inhaled Corticosteroids (ICS)

ICS are applied in patients with a history of repeated exacerbations and/or high levels of eosinophils in COPD. They are more anti-inflammatory and especially in the eosinophilic phenotype or asthma COPD overlap patients. Nevertheless, ICS monotherapy is not recommended because it has a higher risk of pneumonia and little impact

on lung function. Pascoe et al. (2019) in their review of the IMPACT trial have demonstrated that an increased level of blood eosinophil was associated with a greater advantage of ICS-based regimens, specifically triple therapy, compared with dual bronchodilation. This lays stress on the significance of the application of ICS on the basis of biomarkers. Koarai et al. (2021) also demonstrated that the triple therapy (LABA/LAMA/ICS) was much more effective than LABA/LAMA combinations in the exacerbation reduction in moderate to severe COPD. Table 2 shows a simplified decision tool for the exacerbation history and blood eosinophil count to help in initiating the ICS.

Table 2. Criteria for ICS Use Based on Blood Eosinophil Count and Exacerbation History (Tashkin & Wechsler, 2018)

Clinical Scenario	Blood Eosinophil Count	ICS Recommendation
≥2 moderate/severe exacerbations in the past year	>300 cells/μL	Strongly recommend ICS addition
1 moderate exacerbation + high symptom burden	100–300 cells/μL	Consider ICS
Low exacerbation risk	<100 cells/μL	ICS not recommended

4.3 Combination Therapies (LABA/ICS, LABA/LAMA, Triple Therapy)

Combined treatment is applied in order to improve clinical outcomes and the rate of exacerbation. LABA/ICS was once a regular combination but has been dislodged in most places by LABA/LAMA because of the better outcomes and side effects. The introduction of triple therapy (LABA/LAMA/ICS) provides wide-ranging, patient-wide pharmacologic protection of the patient with a high symptom burden and frequent exacerbations. Koarai et al. (2021) compared the triple therapy with the dual combinations and observed that the exacerbation rate was lower and the lung functions were improved and patient-reported outcomes were improved.

The above-mentioned IMPACT trial by Pascoe et al. (2019) has proved the fact that triple therapy is more effective than LABA/LAMA or LABA/ICS monotherapies in reducing the incidence of moderate-to-severe exacerbations especially in patients with high blood eosinophil counts. This observation was also echoed by a meta-analysis by Li et al. (2025) that suggested that triple therapy reduced not only the exacerbation but also all-cause mortality and cardiovascular risks in moderate to severe COPD patients.

4.4 Adjunct Therapies

Phosphodiesterase-4 Inhibitors (Roflumilast)

Roflumilast is an anti-inflammatory agent, which is a PDE-4 inhibitor and is consumed orally and is used in the patients with the chronic bronchitis phenotype, multiple exacerbations and severe airflow limitation. It reduces the level of inflammatory response by increasing the intracellular level of cyclic AMP, thereby preventing the pro-inflammatory cytokines.

Wedzicha et al. (2016) examined its clinical application and observed a considerable decrease in the exacerbation rates and minor improvements in lung functions. Its application is however restricted by its side effects that include weight loss and gastrointestinal symptoms. Timm Wagner and Kenreigh (2005) earlier reported of its early clinical prospect with Roflumilast and found out that it is very effective in the reduction of exacerbation in patients who are already taking bronchodilators but still experiencing frequent symptoms.

Theophylline

Theophylline is a medium strength Bronchodilator, anti-inflammatory, and ant-inflammatory agent and a methylxanthine. Its application has also been limited because of its narrow therapeutic index and the fact that it is toxic but it can be used in low-resource settings or as an add-on therapy with other bronchodilators. Barnes (2013) discussed the contemporary use of theophylline and indicated that it could enhance steroid responsiveness in certain cases of corticosteroid-resistant COPD with the cost of having a meticulous toxicity surveillance plan.

Mucolytics and Antioxidants

Mucolytics e.g. N-acetylcysteine reduce the thickness of the sputum thus facilitating the mucociliary clearance. They are useful in patients who have chronic bronchitis phenotype. They do not belong to major pharmacologic groups, but their adjunctive application may diminish the number of exacerbations in some patients.

Long-Term Antibiotics

They have shown that macrolides (mainly azithromycin) reduce the exacerbation frequency in patients with recurrent infectious exacerbations in long-term treatment. Spagnolo et al. (2013) have also reported that it possesses the anti-inflammatory and immunomodulatory effects, however, they mentioned the risks associated with its usage, such as antibiotic resistance and hearing loss.

The existing pharmacologic treatment of COPD is multidimensional, with bronchodilators as the backbone, ICS, combination drugs, and adjunct agents included in the treatment as a combination of individual risk factors and biomarkers. With the ever-increasing therapeutic armory, it is now of utmost importance to provide more personalized treatment using biomarkers, exacerbation history, and phenotype in the management of COPD. The evidence overview indicates that there is need to personalize the intensity and the class of treatment according to the evolving clinical and biological parameters.

5. Emerging and Investigational Therapies

The advantages of the conventional COPD treatment have become increasingly apparent, and the focus is now on precision medicine and new pharmacologic therapies. The following section describes the new approaches that are promising and are under investigation and target the key molecular, cellular, and inflammatory pathways in COPD.

5.1 Biologic Therapies

Interleukins have been promising as some of the biologic anti-inflammatory agents in COPD eosinophilic inflammation. Anti-IL-5 (mepolizumab, reslizumab) and anti-IL-13 (lebrikizumab) mAbs are also in development to find out how they can inhibit the activation and recruitment of eosinophils.

According to Sharma et al. (2024), eosinophilic COPD has a pathophysiological overlap with severe asthma, but the use of biologics in COPD has not been very successful due to the heterogeneity of inflammatory phenotypes. The trials of IMPACT and METREX implied that the patients with the elevated eosinophil counts might be the most promising patients to treat using anti-IL-5; nonetheless, a more refined biomarker is necessary.

The existing gaps are associated with the prohibitive prices, parental route of administration, and low efficacy in broader COPD phenotypes (Appleton et al., 2024). Individualized selection based on eosinophil cutoffs and genetic profiling is in development to be used to better target the patients. Figure 4 illustrates that the inhibition of IL-5 and IL-13 pathways by using monoclonal antibodies decreases eosinophilic activity, mucus production, and hyperresponsiveness in the airways.

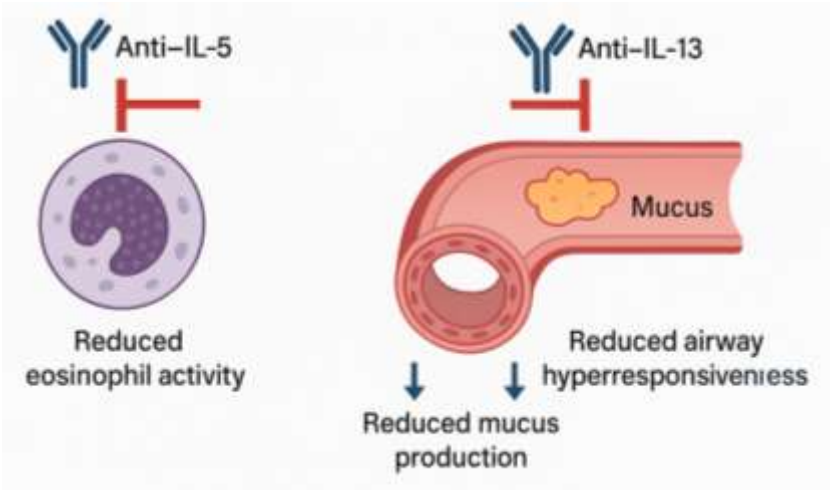

Figure 4. Mechanism of Action of Anti-IL-5 and Anti-IL-13 Biologics in COPD

Anti-IL-5 (mepolizumab, benralizumab) and anti-IL-13 (lebrikizumab) monoclonal antibody-based therapy has been promising in a limited number of COPD patients with high eosinophil counts to enhance the level of eosinophilic inflammation and exacerbation rates. Nevertheless, the clinical effect is not uniform in the wider patient groups. Phase III trials and real-world evidence have not been used consistently, particularly when used in mixed inflammatory phenotype patients. Their cost of treatment is also high; they have to be chosen on the basis of biomarkers, and they have parenteral administration methods, which limit their wide application. Stunningly, even non-pharmacologic population-level interventions such as social distancing during the COVID-19 pandemic have impacted the volume of hospital admissions due to asthma, which is indicative of the role of environmental and behavioral variables in influencing the risk of exacerbating the condition even without the utilization of pharmacotherapy (Toennesen et al., 2022).

These results support the idea of strict patient phenotyping and head-to-head comparisons of the biologics with the conventional anti-inflammatory treatment, i.e., inhaled corticosteroids or PDE-4 inhibitors. Long-term safety evaluations and accuracy in predicting probable respondents will be very critical in ensuring the maximization of the use of biologics in today's management of COPD. The meta-analysis and systematic review of the anti-IL5 therapy in COPD have been noted to have a small and significant effect on the reduction of exacerbation as compared to the placebo, especially in patients with eosinophilic inflammation (Zhang et al., 2021). On the other hand, the anti-IL-13 treatment agents were less clinically important and less effective in treatment. Such comparative results advocate the idea that effective endotype recognition and biomarker-driven therapy choices can be essential in enhancing management in populations with targeted COPD.

5.2 Small Molecule and Kinase Inhibitors

Inflammation-related intracellular signaling cascades are becoming a new target of COPD therapy. Inhibitors of the p38 mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) pathways, especially the small molecule inhibitors, have attracted a lot of attention. Ahmadi et al. (2023) examined the pivotal position of p38 MAPK in the relaying of inflammatory messages of smoking and oxidative stress. Inhibitors of the MAPK could be applied to the treatment of neutrophilic inflammation and cytokine release, but the problem of adverse events and limited duration of action persists.

The PI3K-delta inhibitors are a possible solution to the problem of restoring corticosteroid sensitivity, but at the moment are still at the trial stage. The specificity is what will prevent immunosuppressive effects that are produced by pan-PI3K inhibition (Appleton et al., 2024). The description of new kinase inhibitors, the cellular target, the stage of clinical development, and side effects are provided in Table 3.

Table 3. Summary of Kinase Inhibitors in COPD: Targets, Outcomes, and Limitations (Ahmadi et al., 2023; Appleton et al., 2024)

Inhibitor Type	Target Pathway	Expected Effect	Limitations	Reference
p38 MAPK inhibitors	MAPK signaling	Reduce cytokine production	Short half-life, systemic effects	Ahmadi et al. (2023)
PI3K-δ inhibitors	PI3K signaling	Restore steroid sensitivity	Immunosuppression, specificity required	Appleton et al. (2024)

5.3 Protease Inhibitors and Novel Anti-inflammatory Drugs

The cause of airway remodelling and parenchyma loss that is experienced in COPD is partly due to the imbalance between proteases (e.g., neutrophil elastase, MMPs) and antiproteases. There is an exploration of inhibitors of these enzymes to stop the progression of the disease.

Ahmad et al. (2023) referred to the potential therapeutic effects of a drug that inhibits the action of MMP-9 and neutrophil elastase in their study. The purpose of such agents is to reduce tissue breakdown and hypersecretion of mucus. The problem of off-target effects and specificity is still there, though. Also, the new families of anti-inflammatory agents, like WISP1 inhibitors, are under research to determine their contribution to the macrophage-mediated inflammation. Christopoulou et al. (2024) have claimed that WISP1 contributes to airway fibrosis and may be a drug target in the future.

5.4 Regenerative Therapies and Stem Cell Research

MSCs are regenerative in the sense that they offer immunomodulatory, angiogenesis, and epithelial healing. The umbilical cords, the bone marrow, or the adipose tissue are used to obtain these pluripotent cells.

Nagamura-Inoue and He (2014) highlighted the idea that umbilical cord-derived MSCs have low immunogenicity and accessibility, which is why they are perfect for pulmonary applications. As it was reviewed by Wang et al. (2021), the preclinical models confirm that MSCs reduce the inflammation, enhance the regeneration of the alveoli, and ameliorate lung functioning. The subsequent experiments conducted by Meng et al. (2024) have also confirmed the notion that the procedure of MSCs transplantation can reduce airway remodeling and improve oxygenation in mice with COPD. Clinical trials are in progress, and Marei (2025) warns against unregulated applications, and standardization of dosage, delivery, and outcome measures should be done. Figure 5 illustrates the capability of MSCs to regulate activities of T-cells, cytokine inhibition, and repair of tissue in the lung microenvironment of COPD.

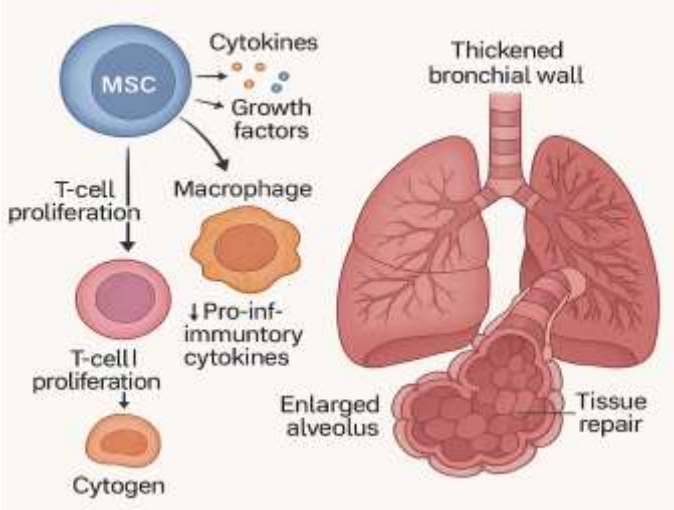

Figure 5. Regenerative Role of MSCs in COPD: Mechanistic Overview

5.5 Gene and RNA Therapies (Experimental)

Gene and RNA-based therapies are still in the early phase, but have great therapeutic potential in regulating COPD inflammation. They are also trying to shut down the pro-inflammatory gene expression through small interfering RNA (siRNA) and antisense oligonucleotides. According to Melim et al. (2022), the nanoformulations are being used to deliver the RNA molecules to the pulmonary tissues, circumventing degradation and poor absorption. There are some siRNAs against IL-8, MMPs, or against components of the pathway of oxidative stress that are in preclinical development. The problems include off-target effects, immune activation, and the delivery through mucus barriers. Nevertheless, it is a major field of precision-related and patient-centered treatment of COPD (Appleton et al., 2024).

6. Personalized Medicine in COPD

Chronic Obstructive Pulmonary Disease (COPD) is increasingly being viewed as a heterogeneous and complicated disease with wide clinical presentation, inflammatory phenotype, and response to therapy. Personalized medicine, or precision medicine, is the approach to treatment that is personalized based on the presence of certain peculiarities of a patient, both biological, genetic, and clinical, as opposed to the conventional types of diseases (Franssen et al., 2019; Moll & Silverman, 2024).

6.1 Heterogeneity of COPD: Phenotypes and Endotypes

The non-homogeneity of COPD is also expressed in the phenotypic grouping, such as emphysema-dominant, chronic bronchitis, frequent exacerbator, asthma-COPD overlap (ACO), and others. The needs of the phenotypes in terms of clinical courses and treatment differ. To take an example, emphysema-dominant patients might be better off with lung volume reduction interventions, whereas ACO patients respond well to inhaled corticosteroids (Han et al., 2010; Agusti & Faner, 2019). The latter also have endotypes behind them: molecular and cellular processes that include eosinophilic or neutrophilic inflammation, remodeling, and systemic immunologic pathways (James & Wenzel, 2007; Bonato, 2023).

6.2 Bimarkers for Therapy Selection

The concept of biomarkers is also employed in an attempt to fill the gap between endotypic knowledge and clinical practice. The number of eosinophils in the blood is the most proven one and defines the sensitivity to corticosteroids in stable COPD and exacerbations (Singh et al., 2014; Tashkin & Wechsler, 2018). The other biomarker that can be employed to detect type 2 inflammation is fractional exhaled Nitric Oxide (FeNO). YKL-40 and IL-6 are also biomarkers that are used to indicate remodeling and systemic inflammation, respectively (Farrell et al., 2024; Panek et al., 2023). Table 4 shows that the new biomarkers can be used to stratify patients and treat them according to the disease processes. The strategies reduce unnecessary exposure to drugs and maximize the outcome of therapy.

Table 4. Key Biomarkers and Their Relevance in Personalized COPD Therapy (Singh et al. (2014); Tashkin & Wechsler (2018); Farrell et al. (2024); Panek et al. (2023))

Biomarker	Associated Endotype	Clinical Relevance	Therapeutic Implication
Blood Eosinophils	Eosinophilic inflammation	Predicts ICS and biologic therapy responsiveness	Guide ICS use and anti-IL-5 agents
FeNO	Type 2 airway inflammation	Helps in identifying ACO and steroid sensitivity	Tailors anti-inflammatory regimens
YKL-40	Remodeling marker	Associated with airway fibrosis	Predicts structural disease progression
IL-6	Systemic inflammation	Correlates with exacerbation risk	Marker for systemic anti-inflammatory therapy
IL-18	Inflammasome activation	Linked with frequent exacerbations	Future target for immune modulation

6.3 Use of Pharmacogenomics

Pharmacogenomics has the potential to transform the treatment of COPD because it will help identify gene variations that affect drug responses. As an example, the reaction to ICS may depend on the polymorphism of the gene GLCCI1, and the reaction to the leukotriene pathway inhibitors may depend on the variation of the genes ALOX5 and CRHR1 (Farzan et al., 2017; Tantisira & Weiss, 2012). Although it has great potential, clinical application is not widespread yet because of logistical barriers and the necessity to validate it in larger populations of COPD patients. Besides, pharmacogenomic tools can be implemented to anticipate adverse reactions, dose adjustment, and avoid treatment failure, enhance patient safety, and personalize treatment (Franssen et al., 2019).

6.4 Trends Toward Precision Therapy

The next breakthrough that has enhanced precision therapy in COPD is the development of molecular diagnostics, big data, and artificial intelligence. The combined proteomic and genomic characterization can ensure that clinicians can classify patients into more specific subgroups, to use monoclonal antibodies, biologics, and new anti-inflammatory agents in a more specific way (Sidhaye et al., 2018; Moll & Silverman, 2024).

Researchers have also found pathways that include inflammasomes that are involved in COPD exacerbation, and this is an area that can be targeted in the future on the basis of immune treatment (Panek et al., 2023). Besides, the fact that the inflammatory processes are similar to those of asthma opens up the possibility of drug repurposing and the development of cross-disease biomarkers (Bonato, 2023). The increasing availability of high-throughput molecular diagnostics and data analytics in real-life will probably continue to make the personalization of COPD treatment the focus of clinical care (Farrell et al., 2024; Kokosi et al., 2018).

7. Current Challenges in Pharmacological Management

Optimal pharmacological management of COPD is a continuous problem, mainly due to low adherence to drugs, inappropriate use of inhalers, polypharmacy, and organizational barriers. Compliance with inhalation therapy is low, and this problem is associated with an incorrect approach and complicated regimens, which significantly predispose to exacerbations and hospitalization (Vauterin et al., 2024; Gregoriano et al., 2018). The cost and access factor also leads to such problems, especially in low-resource patients, who are not well insured and can hardly afford the expensive prices of the drugs, which makes compliance challenging (O'Toole et al., 2022). Another critical matter is polypharmacy, and most patients with COPD have a lot of comorbidities that need to be managed simultaneously, which raises the risks of medication interactions and adverse effects (Alwafi et al., 2024). This is in combination with non-adherence and complications of therapy. Although there is some improvement in disease phenotyping, the fact remains that many patients are treated in a generalized rather than personalized way due to under-recognition of treatable traits, e.g., eosinophilia or chronic bronchitis phenotype (Bryant et al., 2013). The combination of these factors limits the overall efficiency of pharmacological treatment and indicates that particular patient education and policy-based solutions are required as soon as possible. The cause of polypharmacy in COPD is directly linked to the burden of comorbidities that require the use of multiple medications at the same time. Table 5 below presents typical comorbidities of the patients with COPD and the related pharmacological management.

Table 5. Common Comorbidities in COPD and Their Drug Burden (Alwafi et al., 2024)

Comorbidity	Associated Drug Classes
Cardiovascular disease	Beta-blockers, anticoagulants
Diabetes mellitus	Metformin, insulin
Depression/Anxiety	SSRIs, benzodiazepines
Osteoporosis	Bisphosphonates, calcium/vitamin D
GERD	Proton pump inhibitors (PPIs), antacids

8. Future Directions and Research Needs

The novel advancements in the field of Chronic Obstructive Pulmonary Disease (COPD) management point to the fact that paradigm-shifting solutions are needed to help overcome the symptomatic management of the disease. One of the most relevant future trends is the creation of disease-modifying treatments that would change the natural progression of COPD. According to Singh et al. (2025), there are novel agents that target molecular pathways like epithelial-mesenchymal transition and airway remodeling with the potential to slow down the progression of the disease and decrease the morbidity in the long term.

The long-term safety data and real-world evidence (RWE) would be applicable as well. COPD is very heterogeneous, and this is not captured during clinical trials in practice. Ahmed et al. (2025) note that the development of inhalable nanomedicines is necessary, which would not only provide targeted delivery but would be effective in real-life populations with comorbidities. This is the evidence required to attain higher practicality and sustainability of outcomes. Evidence from the real world also indicates that behavioral interventions such as social distancing have been contributing to important decreases in disease exacerbations, and therefore, the impact of external factors cannot be overlooked (Toennesen et al., 2022). Due to the shift in technology, care models are reorganized. The smart monitoring systems and the digital inhalers have become possible measures to enhance adherence and clinical outcomes. Chan et al. (2021) explain that such devices monitor the use of inhalers, give feedback, and allow physician-patient communication, which allows making changes to treatment in real-time. At the same time, Xiroudaki et al. (2021) introduce the issue of the dry powder inhaler with embedded sensors that help to promote patient adherence and dose accuracy.

The future treatment of COPD is also a promising innovation in the sphere of nanotechnology. Singh (2025) addresses nanomaterials based on microbiome, which have the advantage of being biocompatible and offering site-specific drug delivery, which reduces the exposure to the systemic level and increases the targeting to the lungs. These compositions may be the focus of the next-generation inhalation products. The implementation of personalized care models, namely the combination of clinical, genomic, and behavioral data, will most likely revolutionize COPD treatment. Ahmed et al. (2025) encourage individualized models of treatment that are adaptive and data-driven in terms of phenotypes and outcomes of the treatment. In general, future research must be aimed at disease-modifying drugs, utilize digital technologies, prove the effectiveness of the real-world treatment, and embrace precision-based models to revolutionize COPD treatment.

9. CONCLUSION

Chronic Obstructive Pulmonary Disease remains a challenge to both clinicians and researchers because it has a progressive character, is pathophysiologically complex, and has clinical heterogeneity in its presentation. There has been a lot of change in pharmaceutical management with a shift towards target-specific and precision bronchodilating therapy. The introduction of long-acting bronchodilators, inhaled corticosteroids, and combination regimens has had a major impact on the enhancement of lung function, control of symptoms, and decrease in the frequency of exacerbations. The improved knowledge of the COPD phenotypes and endotypes has helped in the more precise treatment. Blood eosinophils and FeNO are now increasingly used as biomarkers to stratify patients and incorporate them into algorithms of treatment. The maximization of personalized treatment opportunities through the establishment of digital inhalers and pharmacogenomic-based innovations that offer immediate feedback and improved compliance tracking is also possible. Although there are such innovations, there are still challenges. Inadequate compliance with the drug, incorrect use of the inhaler, and interaction associated with polypharmacy remain factor that undermines the benefits of treatment, especially in elderly patients. In addition, financial barriers and inadequacies in the process of identifying characteristics that can be treated act as a barrier to applying precision methods in practice. It is interesting to note that recent systematic reviews and meta-analysis studies have indicated that further comparisons are required between

biologics and conventional anti-inflammatories. Although the possibility of biologics targeting the eosinophilic pathway in reducing exacerbation rate in specific phenotypes is quite promising, they must be subjected to testing against inhaled corticosteroids and PDE-4 inhibitors to demonstrate superiority, cost-effectiveness, and safety in the long term. The next research direction must be the identification of disease-modifying agents capable of reversing the airway remodeling and chronic inflammation. Similar initiatives are needed to make sure that digital tools, long-term outcome tracking, and equal access to care are involved. Translational innovations and multidisciplinary strategies will continue to play a significant role in changing the COPD therapy from generalized protocols to a truly individualized one.

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