IJMPR, 2026, 10(1), 30-36 ISSN: 2319-5878

INTERNATIONAL JOURNAL OF MODERN PHARMACEUTICAL RESEARCH

www.ijmpronline.com

Review Article
Impact Factor: 6.669
Coden USA: IJMPR3

EVOLVING PERSPECTIVES IN COPD: EMERGING THERAPIES AND FUTURE DIRECTIONS

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Article Received on: 25/11/2025 **Article Revised on: 05/12/2025** **Article Published on: 01/01/2026**

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https://doi.org/10.5281/zenodo.18107208

How to cite this Article: Prateek D.T.1, Kavitha V. Dongerkery2*, Pradnya Deolekar3, Atharva Dahibhate4, Movva Navya5, Akash Sinha6, Veena Rane7, Yuvraj Sawant8 (2026). Evolving Perspectives In Copd: Emerging Therapies And Future Directions. International Journal of Modern Pharmaceutical Research, 9(12), 30–36.

ABSTRACT

Background: Chronic inflammation, airway remodelling, and irreversible airflow limitation are the main causes of Chronic Obstructive Pulmonary Disease (COPD), which continues to be a major cause of morbidity and mortality globally. The management of COPD remains difficult because of the disease's heterogeneity, underdiagnosis, and limited response to treatment in some phenotypes, even with the availability of traditional bronchodilators and corticosteroids. The purpose of this review is to highlight new pharmacological treatments that have the potential to revolutionise the treatment of COPD and to provide an overview of recent developments in our understanding of its pathophysiology. **Summary:** We now have a better understanding of the intricate pathophysiology of COPD thanks to recent discoveries in molecular and cellular mechanisms, microbiome interactions, and genetic and epigenetic regulation. Inadequate spirometry use and a lack of awareness of non-tobacco risk factors like air pollution and recurrent respiratory infections continue to impede early diagnosis. Pharmacological advancements include new drugs like ensifentrine, a dual PDE3/4 inhibitor with bronchodilatory and anti-inflammatory properties, and triple-therapy inhalers (LAMA/LABA/ICS), which provide better symptom control and fewer exacerbations. Mepolizumab and dupilumab, two biologic treatments that target type-2 inflammation, have shown promise in treating eosinophilic COPD phenotypes. Astegolimab, itepekimab, and tanimilast, future agents being studied, are encouraging developments in precision-based therapeutic strategies. **Conclusion:** The treatment of COPD is moving towards phenotype-driven, individualised care that focusses on the underlying inflammatory pathways rather than just the symptoms. To improve patient outcomes and quality of life, more research is needed on biomarkers, regenerative techniques, and disease-modifying therapies.

KEYWORDS: COPD, emerging therapies, ensifentrine, dupilumab, mepolizumab, triple therapy.

1. INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by progressive partially reversible airflow obstruction, chronic inflammation, airway remodeling, and excessive mucus production.[1] About 10.3% of people worldwide have COPD and causes up to three million deaths annually, with almost 89 million diagnosed cases in India.[2] Chronic inflammation brought on by extended exposure to harmful particles or gases-most frequently cigarette smoke is linked to structural alterations in the lungs. Lung recoil is reduced and airways narrow as a result of chronic inflammation. Sputum production, coughing, and dyspnoea are common symptoms of the illness. From respiratory failure to a lack of symptoms, symptoms can vary widely.[3] The most common combination of respiratory failure and acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is linked to high rates of morbidity and mortality. The prognosis for treatment is significantly impacted by the poor functional reserve capacity of several organs in elderly patients.[4] The pathophysiology and diagnosis of early COPD have drawn more attention due to the disease's high prevalence and progressive nature, with the hope that improved long-term outcomes will result from a better understanding and diagnosis of early disease. Treating COPD has significant financial impacts on health care systems; it accounts for approximately 4% of all public hospital annual admissions in Hong Kong and is a leading cause of hospital readmissions.[5,6,7,8] The Global Initiative for Chronic Obstructive Lung Disease strategy document recommended guidelines for managing comorbidities, suggesting it should be personalized for the individual.[9] Suboptimal management of COPD reduces patients' quality of life and increases their risk of acute exacerbation of COPD, leading to hospital admission and readmission – and increased risk of mortality. non-adherence to COPD medication, incorrect inhaler technique, and/or selection of appropriate inhaler device worsens clinical and economic outcomes.[10,11] Our article aims to elaborate all the available medications and also focus on the recent advances available in today's world.

2. Pathophysiological Understanding

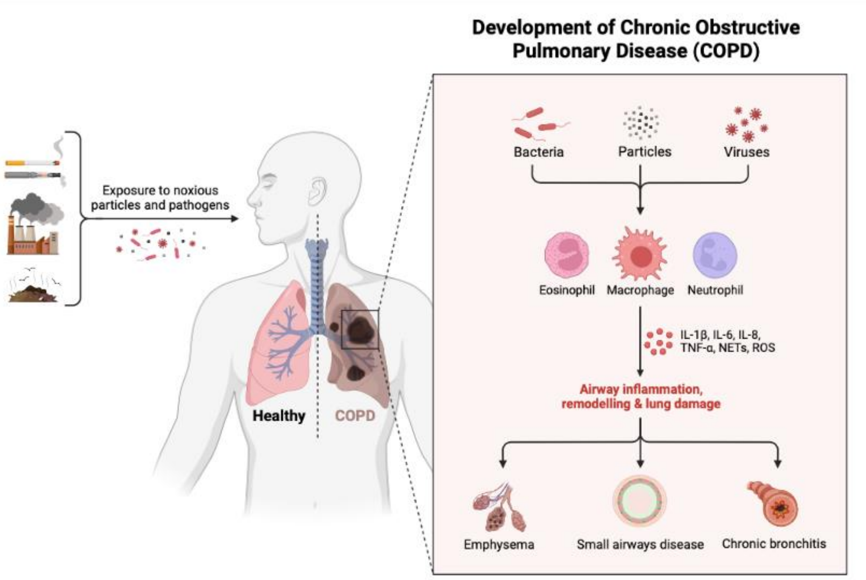

Figure no 1: Illustrating the pathophysiology of COPD.

Treating COPD has always been a difficult task for the clinicians because of its complex pathology and various number of symptoms associated. Some of the pathophysiological explanations can be given through molecular and cellular mechanisms, microbiome and immune interactions, genetic and epigenetic functions, tissue remodelling and repair mechanisms.[12]

In industrialized nations, direct inhalation of tobacco products has been long recognized as the principal causative exposure leading to COPD. In developing nations, by contrast, air pollution (both indoor due to biomass fuel use and outdoor) is a major contributor.[13,14] Nearly all information on lung pathology in COPD is derived from studies of smoking-related illnesses in areas with high sociodemographic indices (SDI). The United States is one high-SDI country where residents' risks of developing COPD are not evenly distributed; rather, they are influenced by a complex interplay of racial/ethnic, socioeconomic, and geographic factors.[15]

Loss of local innate immune defences is one of the main causes of small airways disease, a prominent early COPD pathology

Adults are said to have small airways, which are defined as those with a diameter of less than 2 mm, distributed between the fourth and fourteenth (mean eighth)34 or eighth and twenty-second (mean fourteenth)35 generations of airway branching. This area, which is farther from the point of maximal airway resistance, is distinguished by rapidly increasing total cross-sectional airway area but decreasing individual airway diameters. For a number of reasons, these distal airways are particularly vulnerable to harm from oxidative stressors that are inhaled, such as smoking and air pollution. The transition from laminar or turbulent flow to diffusion in gas transport occurs in the small airways, which promotes the deposition of fine particles and may lengthen exposure to gas-phase irritants.[16] Small airway changes are the most well-studied pathology in COPD, and they are probably the main smoking-induced lesion in the majority of patients who develop severe airflow obstruction.36 In the 1960s, sophisticated retrograde catheter studies showed that small airways are the primary site of air flow obstruction in the human lung. In advanced emphysema, their contribution to total peripheral resistance increases four to forty times.[17] Smoking causes the airway epithelium to be rewired in several ways, which lowers the immune defences of the small airways and is the direct cause of SAD.[18]

3. Challenges of COPD Detection

A) Lack of Spirometry Use

Spirometry is a crucial diagnostic and treatment tool for COPD. Nonetheless, a significant contributing factor to the underdiagnosis of COPD is the underutilisation of spirometry. Just 36.7% of the 93,724 newly diagnosed COPD patients in a recent study by Joo et al. underwent spirometry.[19] In Salzburg and Austria, Lamprecht et al. discovered that just 67.6% of participants with a reported diagnosis of COPD had previously undergone a spirometry. Just 56.2% of Italians with COPD who have been diagnosed by a physician have ever undergone a spirometry in a primary care setting. Lack of experience in interpreting spirometry, the high cost of the spirometer, and patients' inability to pay for the test, particularly in primary care or resource-constrained settings, were the causes of the underutilisation of spirometry. To get past this obstacle, alternative instruments for environments without spirometry are required.

B) Overlooking Other Risk Factors for COPD

Old age and tobacco use have long been linked to COPD. Nonetheless, non-tobacco risks are increasingly being blamed for the burden of COPD, and during the next 20 years, these risk factors are predicted to overtake tobacco use. Genes (G) and the environment (E) interact dynamically, cumulatively, and repeatedly throughout life to cause COPD person's lifetime (T), which may alter their normal ageing or developmental processes and/or result in lung damage (GETomics).[20] All things considered, exposure both indoors and outdoors is highly associated with an increased risk of COPD, highlighting the necessity for legislators to enact policies that will lower air pollution and protect public health. Numerous factors, such as recurrent respiratory infections, dietary and socioeconomic factors, and exposure to ambient tobacco smoke, can contribute to impaired lung growth in childhood and early adulthood. To improve lung health throughout one's life, efforts must be made to limit early exposure to risk factors for COPD and impaired lung growth.[21,22]

C) Missing Early Signs of COPD

Undiagnosed patients may have a lower disease burden, according to earlier research, which can considerably postpone the diagnosis of COPD. According to Lamprecht et al., people with mild to moderate airway limitation have a much higher chance of having undiagnosed COPD than people with extremely severe limitation. One This suggested that undiagnosed COPD is substantially positively correlated with milder airway limitation. In addition, people with undiagnosed COPD have fewer symptoms, like chest pain and wheezing, than people with a diagnosis. According to a previous meta-analysis study, people with undiagnosed COPD experienced fewer respiratory symptoms and less severe airflow obstruction than people with diagnosed COPD.[23] This might be the result of patients ignoring their symptoms, not telling their doctor about them, or doctors failing to notice subtle early warning signs. In the UK, for example, a retrospective analysis of a clinical cohort showed that 85% of patients sought primary care for lower respiratory symptoms within five years prior to receiving a diagnosis of COPD., therefore raising awareness of COPD among both patients and doctors is essential.

4. Advances in Pharmacological Management of COPD

A) Triple inhalers

Delivering a combination of the three inhaled medications (LAMA, LABA, and ICS) is known as "triple therapy." Triple therapy can be prescribed as a single inhaler which delivers all three drugs in one dose or as multiple inhalers which deliver separate doses of each drug.

Long-Acting Muscarinic Antagonist, or LAMA targets smooth muscle M_3 receptors in the airways and acts by preventing acetylcholine-induced bronchoconstriction, leading to bronchodilation. Other effects include a decrease in air trapping, an improvement in airway quality, and a reduction in mucus secretion. Whereas Long-Acting β_2-Agonist, or LABA targets smooth muscle β-adrenergic receptors in the airways and acts by Activating adenylate cyclase which increases cyclic AMP and leads to smooth muscle relaxation resulting in bronchodilation. Additional benefits include a decrease in dynamic hyperinflation and an improvement in mucociliary clearance. Additionally Inhaled corticosteroid, or ICS targets immune cells and airway epithelial glucocorticoid receptors and acts by reducing eosinophilic and neutrophilic inflammation and downregulates pro-inflammatory cytokines (e.g., IL-8, TNF-α). As a result, airway inflammation is decreased, and exacerbations occur less frequently and with less severity.[24,25]

Available combinations of triple therapy inhalers are budesonide (ICS) + glycopyrrolate (LAMA) + formoterol fumarate (LABA); (beclomethasone (ICS) + formoterol (LABA) + glycopyrrolate (LAMA); fluticasone (ICS) + umeclidinium (LAMA) + vilanterol(LABA).

B) Ensifentrine

- Ensifentrine is a novel, selective, dual phosphodiesterase (PDE)3 and PDE4 inhibitor with bronchodilator and anti inflammatory effects. A variety of respiratory processes are targeted by phosphodiesterase (PDE)3 and PDE4 inhibitors. PDE3 mediates bronchial tone by controlling cAMP and cGMP in airway smooth muscle. PDE4 controls cAMP and plays a role in the activation and migration of inflammatory cells as well as the stimulation of the cystic fibrosis transmembrane conductance regulator in bronchial epithelial cells. When compared to inhibition of either PDE3 or PDE4 alone, dual inhibition of PDE3 and PDE4 has demonstrated enhanced or synergistic effects on airway smooth muscle contraction and suppression of the inflammatory response.[26] This dual mechanism of action makes it a promising treatment strategy for inflammatory and obstructive respiratory tract diseases, including asthma, cystic fibrosis, and COPD. Out of the 11 PDE isoforms, Ensifentrine is a new, selective, dual inhibitor of PDE3 and PDE4 that combines effects on inflammation, airway smooth muscle, and stimulation of the transmembrane conductance regulator in cystic fibrosis into a single substance.[27,28] The ENHANCE trials (Efficacy and Safety of Nebulized Ensifentrine in COPD) done over 24 weeks ensifentrine-treated patients reported significant improvements from baseline in symptoms that were consistent across E-RS, TDI, and rescue medication use measures, as well as quality of life.[29] Hence it would be a valuable and complementary addition to the limited available treatment mechanisms for patients with COPD.

C) Dupilumab

Dupilumab is a dual inhibitor of IL-4 and IL-13 signaling, sources of both local and systemicinflammation. It has been approved for use in numerous type 2 inflammatory diseases—atopic dermatitis (AD), asthma, chronic rhinosinusitis with nasal polyposis (CRSwNP), eosinophilic esophagitis (EoE), and prurigo nodularis. Monocytes, TH0 cells, TH2 cells, fibroblasts, eosinophils, and B cells all have the type 1 receptor. Monocytes, fibroblasts, eosinophils, activated B cells, epithelial cells, goblet cells, and smooth muscle cells all have the type 2 receptor. By blocking the IL-4/IL-13 axis, a major contributor to type 2 inflammation, dupilumab reduces it. TH2 cell differentiation and clonal expansion are stimulated by IL-4, which further increases IL-4 and IL-13 production. Several type 2 inflammatory processes, including fibroblast collagen production, B cell isotype class switching to IgE, and eosinophil trafficking to tissues, are facilitated by IL-4 and IL-13. Smooth muscle cell contractility, goblet cell hyperplasia, and mucus production are all largely caused by IL-13. The IL-4/IL-13 axis drives many of the foundational pathways common among type 2 inflammatory diseases, which emphasizes the therapeutic power of simultaneously blocking IL-4 and IL-13 signaling with dupilumab. Type 2 inflammation induces common biological effects— epithelial hyperplasia, basal membrane thickening, barrier disruption, and inflammatory infiltrate—that cause symptoms in the affected tissues across the spectrum of type 2 inflammatory diseases. Dupilumab is available in various strengths as a pre-filled syringe (300 and 200 mg) or as a pre-filled pen (300 and 200 mg) for subcutaneous injection. The pre-filled syringe is approved for use in patients 6 months and older, while the pre-filled pen is for patients 2 years and older in the US.[30] Dupilumab-treated COPD patients with type 2 inflammation, as shown by increased blood eosinophil counts, experienced fewer exacerbations and improved lung function and quality of life.[31]

D) SMART (Single Maintenance and Reliever Therapy)

SMART (Single Maintenance and Reliever Therapy) or MART (Maintenance and Reliever Therapy) are a next-generation asthma treatment containing an ICS (inhaled corticosteroid) with formoterol (long-acting beta agonist) combined into one inhaler. SMART/MART includes formoterol due to its ability to be fast-acting for rapid onset of asthma symptoms (similar to a short-acting beta agonist) with a longer lasting effect. This SMART treatment option may be prescribed to those with moderate to severe persistent asthma, as a daily controller medication (ICS/ formoterol) and/or to treat rapid onset of symptoms as a quick relief medicine Variety of inhalers available for treatment of COPD.[32]

5. Future Directions

A) Mepolizumab

Mepolizumab is a humanized monoclonal antibody that targets interleukin-5, a cytokine that plays a central role in eosinophilic inflammation, which is present in 20 to 40% of patients with chronic obstructive pulmonary disease. A recent phase 3 double-blind, randomized, placebo-controlled trial, patients with COPD, a history of exacerbations, and a blood eosinophil count of at least 300 cells per microliter who were receiving triple inhaled therapy showed that annualized rate of moderate or severe exacerbations was significantly lower with mepolizumab than with placebo, time to the first moderate or severe exacerbation was longer with mepolizumab than with placebo.[32]

Figure no 2: Showing various combinations of inhaler therapies available.

B) Astegolimab

Astegolimab is a selective ST2 IgG2 monoclonal antibody which has implicated role in airway inflammation and infection. A recent Phase 2a, placebo comtrolled trial has shown no significant improvements in exacerbation rate of COPD but did improve health status of the patients.[33]

C) Itepekimab

Genetic data implicate IL-33 in asthma susceptibility. Itepekimab, a monoclonal antibody targeting IL-33, demonstrated clinical activity in asthma, with potential in chronic obstructive pulmonary disease (COPD). In a recent Phase 2a, randomised, double-blinded trial, it was shown that itepekimab reduced exacerbation rate and improved lung function in former smokers with COPD. Two phase 3 clinical studies are ongoing to confirm the efficacy and safety profile of itepekimab in former smokers with COPD.[34]

D) Tanimilast

Tanimilast a PDE 4 inhibitor has currently completed a phase II clinical development program and started Phase III as a treatment to reduce the risk of exacerbations in COPD patients with chronic bronchitis and a history of exacerbations, as an add-on to triple therapy.[35]

6. CONCLUSION

The management of chronic obstructive pulmonary disease (COPD) is about to enter a transformative era, moving away from symptom-based care and towards precise, phenotype-driven care. A deeper comprehension of the disease's intricate immunopathology is reflected in the development of novel treatments, which range from dual PDE inhibitors and triple-inhaler combinations to biologics that target type 2 inflammation. Biologic therapy for COPD, especially for eosinophilic phenotypes, began with drugs like dupilumab and mepolizumab. New inhaled modalities and anti-inflammatory pathways, on the other hand, promise to increase options for patients who experience frequent exacerbations or persistent symptoms.

Future studies should focus on improving non-steroidal anti-inflammatory drug regimens, investigating regenerative and disease-modifying therapies, and honing biomarker-guided treatment selection.

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