REVIEW PAPER

Chronic Obstructive Pulmonary Disease: A Review on Gene-Environment-Time (GxExT) Interactions, Lung Function Trajectories and Clinical Implications

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) continues to be a leading cause of ill health globally, with a prevalence of about 10% of the adult population worldwide and is responsible for more than 3.2 million deaths each year. A 44% increase worldwide in the prevalence of COPD from 1990 to 2010 is evident from the literature, and smoking is not the only factor responsible for this increase. The etiology of COPD relates to complex interactions between genetic susceptibility, environmental factors and life course influences. The classic model of COPD that associates it with smoking-related accelerated lung decline has been replaced by a more comprehensive model that takes into account polygenic factors, epigenetic changes, lung developmental impairments and different lung dysfunction trajectories. Recent evidence suggests that 20 to 40% of COPD cases can be found in people who have never smoked; therefore, the authors that write in the gene-environment-time (GxExT) framework point to ambient air pollution, biomass fuel, early-life infections and the occupational exposures as the factors responsible for the disease. On one hand, significant steps have been made in radiology, including parametric response mapping (PRM), to identify early small airway disease that precedes spirometric obstruction. On the other hand, biomarkers such as CRP, fibrinogen, eosinophils and sRAGE provide a means to enhance diagnostic accuracy and personalize therapy. Apart from inhaled bronchodilators and corticosteroids, treatment modalities now include precision-based interventions using eosinophil counts, long-term macrolides, phosphodiesterase-4 inhibitors and emerging biologics. There is also a list of non-pharmacological interventions that are useful in COPD management, such as pulmonary rehabilitation, lung volume reduction surgery, long-term oxygen therapy for severe hypoxemia and home non-invasive ventilation to be used selectively. This review mainly focuses on Gene-Environment-Time (GxExT) Interactions in COPD, revised understanding of lung function trajectories, pathophysiology, diagnosis and therapeutic approaches of COPD.

Keywords: Chronic Obstructive Pulmonary Disease, Gene - Environment - Time (GxExT) Interactions, Lung Function Trajectories, Pulmonary Rehabilitation, Spirometry

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Introduction

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) was identified as a major global health problem, mainly because of its widespread occurrence and rising incidence, as well as, considerable social and economic consequences [1]. According to epidemiological evidence, COPD is responsible for about one-tenth of the total adult population all over the world and this burden is getting higher partly due to aging of the population [2].

An Integrated Paradigm

The concept of chronic obstructive pulmonary disease (COPD) as one single entity, mainly caused by

smoking and characterized by accelerated lung function decline in older men was considered obsolete and insufficient [3,4]. To a large extent, recent studies backed this idea and now they saw COPD as a genetic disorder with a significant epigenetic contribution [5-8]. Besides smoking, a number of environmental factors were also identified as risks, and their influence was shown to accumulate and interact during the life span, affecting not only the development, but also the maintenance, repair and aging of the organ [9].

Beyond Smoking: Gene-Environment-Time (GxExT) Interactions in COPD

The analysis of epidemiological data led to the conclusion that out of the total number of COPD patients globally 20-40% were never smokers, therefore the risk factors other than tobacco exposure were of greatest concern [10]. Regardless of the fact that smoking continues to be the main cause, the additional adverse environmental effects could not be ignored. Research in a large population-based cohort in Austria by Kohansal et al, 2019 [11] found that several environmental factors were not only associated with deteriorated lung function but also had different impacts on various age groups and accumulated in a complicated manner along with increasing age [12]. The authors concluded that just like other chronic diseases, the cause of COPD cannot be solely attributed to gene-environment (GxE) interactions. The temporal dimension, however, turned out to be a very important element as the same GxE interactions were found to have different effects at different life stages. This gene-environment–time (GxExT) concept helped to understand COPD pathogenesis in a more detailed way and pointed out that research and prevention should be life course based [13].

Environmental Factors

Besides tobacco smoking that continued to be the major risk factor for COPD, a few environmental exposures were also blamed for the disease development and progression [14,15]. Household air pollution, particularly from indoor biomass burning, appeared to be of significance in many residents [16].

In a large Chinese cohort who are never-smoking, for cooking the solid fuels use was associated with increased hospital admission risks and mortality [17]. However, these findings remained inconclusive. For example, a rural Malawi study (2019) [18] accredited predominantly to former or current smoking, a history of tuberculosis, or exposure to carbon monoxide and it didn't demonstrate measurable benefits from the adoption of cleaner stoves. These observations suggested that, the environmental factors impact in COPD, might have been weaker compared to tobacco smoking [19].

Ambient air pollutants exposure for long-term was also reported to influence COPD progression. Higher levels of fine particulate matter and ambient ozone were related to CT-detected emphysema progression more rapidly for over a 15-year period in the lung study of MESA (Multi-Ethnic Study of Atherosclerosis). Moreover, faster lung function decline over 10 years by exposure to ozone was predicted [20]. Although fatality concerned to fine particulate matter showed a decline in the past decade [21], air pollution continued to be associated with COPD and other non-infectious pulmonary diseases [22]. Evidence from the London COPD Cohort, which monitored exacerbations over a 20-year period, indicated that elevated ambient nitrogen oxides were linked to an increased risk of subsequent viral-type exacerbations, which also tended to last longer [23].

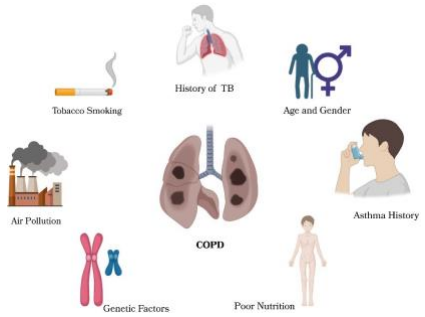

Figure 1: Factors effecting the COPD

Revised Understanding of Lung Function Trajectories

The Fletcher and Peto model had traditionally been elucidated as suggesting that decrease in lung function began at approximately 25 years of age. This interpretation, however, represented the original data misreading. Themselves, the authors had admitted that childhood experiences resulting in lung function reduction at peak during adolescence could also predispose individuals to COPD later in life, even in the presence of a normal rate of decline [24].

Approximately five years ago, Lange et al, (2015) [25] revisited this concept in three large independent cohorts: the Lovelace Smokers Cohort, the Framingham Offspring Cohort and the Copenhagen City Heart Study. The findings of Lange et al, (2015) demonstrated that nearly half of the patients with COPD followed the classical trajectory of accelerated decline in lung function described by Fletcher and Peto, whereas the remaining half of the COPD patients never attained normal lung function at peak at around 25 years of age and COPD was developed despite a usual

subsequent decline in rate. These results reflected the original hypothesis of Fletcher and Peto, which had been underappreciated in subsequent years.

More recent population-based studies further revealed that impaired lung development was not uncommon, being present in approximately 4-12% of the general population [26-28]. These findings contributed to the establishment of the lung function trajectories concept in COPD, highlighting the role of both early-life lung development and later-life decline in disease pathogenesis [29].

Studies on Endophenotypes of COPD

COPD was reported to be influenced by both determinants of exogenous factors and intrinsic factors. Intrinsic factors primarily comprised genetic [30,31] and epigenetic influences [32,33], whereas exogenous factors included a range of non-host determinants [34-36] such as pathogens and environmental pollutants. Initially, the researchers mainly focused on a single candidate gene [37-40] or age group [41,42], which was usually studied with or without prior association evidence with COPD.

Several studies converged on the SERPINA1 gene in line with earlier observations [43]. This gene was responsible for alpha-1 antitrypsin, a neutrophil elastase inhibitor, whose genetic deficiency was identified as a monogenic disorder that showed respiratory features similar to COPD [44]. The discoveries led to the involvement of intrinsic factors in the mechanisms of COPD and genetic susceptibility was highlighted as a determinant of the disease progression.

Epithelium of Airway

Against the inhaled irritants the role of epithelium of airway was investigated as the first line of defence in various studies. Petit et al (2019) [45], used cell derivatives of well-differentiated airway epithelium from smokers, non-smokers and COPD patients, described that the cell signalling of intracellular calcium was altered in cells from both COPD patients and smokers. Since intracellular calcium was essential for regulating mucociliary clearance, the authors demonstrated that the calcium channel component ORAI3 (ORAI calcium release–activated calcium modulator) played a critical role in this process. Down-regulation of ORAI3 impaired ciliary beat frequency [46], thereby reducing mucociliary clearance, a phenomenon frequently observed in COPD airways.

Similarly, Feldman et al (2019), also employing well-differentiated airway epithelial cells [47], identified signalling of transforming growth factor-β (TGF-β) through SMAD pathways as a key regulator of mucous cell differentiation. The epithelial differentiation was suppressed by this pathway and functioned as a gatekeeper, suggesting a possible therapeutic target for limiting hyperplasia of goblet cell in COPD [48]. However, the dual role of TGF-β in airway remodelling and fibrosis raised concerns regarding the clinical applicability of such an approach.

The significance of the epithelial barrier was first pointed out in the research work on the effects of inhaled toxicants. Lin et al (2019) [49] examined whether vapor of e-cigarette disrupted function of epithelium in a manner similar to conventional cigarette smoke. Their findings demonstrated that vapor of e-cigarette reduced epithelial barrier integrity and altered ion transport through the cystic fibrosis trans-membrane regulator (CFTR). Although the consequences on other ion channels were not explored [50], these results provided evidence of potentially harmful consequences associated with e-cigarette exposure.

With respect to the alveolar epithelium, the alveolar epithelial type II cells exposure to extract of cigarette smoke induced the up-regulation of S100A8 (S100 calcium-binding protein A8), which conferred protection against apoptosis [51]. In contrast, the down-regulated S100A8 expression was found in cells derived from emphysema patients, suggesting a potential defensive role of this molecule in the COPD pathogenesis [52].

Pathophysiology

Understanding of disease progression COPD was historically derived from the seminal observations of Fletcher and Peto. In their prospective study in West London of approximately 800 men of age 30-59 years, followed every six months over an eight-year period beginning in 1961 [53], forced expiratory volume in one second (FEV_1) was shown to decline continuously, with an accelerated rate of decline observed with aging. People who did not smoke showed a slow decrease in their health condition and very rarely developed obstruction of the airflow. On the other hand, smokers were divided into two groups, namely "susceptible" and "non-susceptible." Those non-susceptible smokers showed a decline in FEV_1 similar to that of a non-smoker, while the susceptible group had the decline happening in a faster way, thus the obstruction of airflow, disability and premature death were the consequences of their condition. This pattern set up the dominant view that inhaling particulate matter especially, the cigarette smoke was the main reason that

the age-related decline in lung function of the individuals who were the most vulnerable to this would occur faster.

This paradigm was hardly ever disputed until contemporary long-term studies provided new perception at the lifetime lung function trajectories and changed the perception. Lange et al, 2015 identified three large groups of people, described two major pathways that could lead to COPD: (i) after adolescence the attainment of normal peak lung function is followed by an accelerated FEV_1 decline and (ii) during the developmental period, failure of lung function due to reasons of which one is still oblivious, thus one develops COPD despite experiencing a normal age-related decline [54]. Studies on birth and later growth cohorts additionally pointed out that lung function paths from cradle to early adulthood were determined by early-life factors that were mostly manageable like prematurity, passive and active smoking, recurrent lower respiratory infections in childhood and asthma persistence. The researchers emphasized the importance of intervention at an early age as a way to maximize lung growth and lessen the risk of COPD during old age [55-58].

At the cellular level, among the epithelium, basal epithelial cells genetic reprogramming was considered to be one of the earliest histological changes after cigarette smoke exposure. Basal epithelial cells, which are a central organ of the epithelial restructuring and the lung defense system of the organism [59,60], showed changes leading to the squamous metaplasia, the cilia dysfunction, the goblet and the basal cell hyperplasia and the excessive production of mucus. All of these changes facilitated the development of a pro-inflammatory airway microenvironment that was prone to further damage and infection [61]. The studies of gene expression in the epithelium of the respiratory tract from smokers and nonsmokers, smokers with COPD showed the decrease in the distal parts of the airway epithelium and increase in the proximal of the smokers, especially in those with COPD. The activation of the epidermal growth factor receptor on the basal cells was implicated in the mediation of this phenomenon, thus it being a potential therapeutic target [62].

Cigarette smoke-induced epithelial reprogramming had a profound effect not only on the cells of the epithelium but also on the composition of airway surface liquid, especially its water and mucin content. As mucins are one of the major products of goblet cells, mucins appeared to have been significantly elevated in the sputum samples of COPD smokers when compared with the healthy controls and were linked to the chronic bronchitis phenotype [63]. These results implied that the concentration of mucins could serve both as a therapeutic target and as a biomarker. In a normal lung, epithelial cells of the small airway make two monomeric immunoglobulin A(IgA) subunits and release them into the lumen through the polymeric Ig receptor (pIgR) [64]. When pIgR separates the secretory IgA (SIgA) it provides the frontline defense against bacterial invasion. Cigarette smoking decreased pIgR expression and hence, induced localized SIgA deficiency which in turn led to increased chances of bacterial infection. The deficiency caused the activation of nuclear factor-κB leading to airway inflammation that persisted over time. Alterations in the airway microbiome were also reported, potentially explaining why only a subset of smokers progressed to COPD; however, the specific microbial drivers and their temporal contributions to disease progression remained uncertain.

Emerging evidence suggested that bacterial invasion might act as a trigger for airway remodelling, which in turn could precede emphysema development. Contrary to earlier assumptions that small airways contributed minimally to airway resistance totally [65], studies from the late of 1960s and early of 1970s established that in fact, in COPD the increased resistance of predominant site were small airways. Structural and functional abnormalities were detectable even in the absence of overt morphological lung disease [66]. Histological and computed tomography (CT) studies further demonstrated narrowing of distal airway and eventual airway loss during the early stages of disease, preceding the development of emphysema [67].

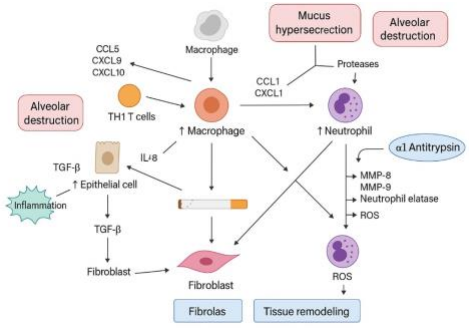

Figure 2: Pathophysiology of COPD

Diagnosis

COPD remained both misdiagnosed frequently and under diagnosed in clinical practice. Analyses from the National Health and Nutrition Examination Surveys (NHANES) illustrated that

individuals of more than 70% with obstruction of airway chronically on spirometry did not carry a fixed COPD diagnosis [68]. Similarly, an evaluation across five health plans revealed that only patients of 32% with a new presumed COPD diagnosis underwent spirometry for diagnostic confirmation [69]. In 2016, the US Preventive Services Task Force reaffirmed its recommendation against diagnosing asymptomatic adults with spirometry, citing insufficient confirmation that screening improved clinical outcomes for long-term [70]. A prominent warning was that a lot of patients covered their symptoms by holding back from exertional activities or by attributing their limitations to getting older or lack of conditioning. Consequently, case-finding approaches were increasingly explored in preference to population-based screening [71]. One such strategy combined a five-item questionnaire (CAPTURE: COPD Assessment in Primary Care to Identify Undiagnosed Respiratory Disease and Exacerbation Risk) with peak expiratory flow [72]. This practical, affordable tool, under evaluation in primary care populations proved perceptive and certain in at-risk patients' identification suitable for confirmatory spirometry.

The diagnostic COPD definition required post-bronchodilator spirometry showing obstruction of airflow persistently, defined as a FEV_1/FVC ratio < lower limit of normal (LLN) but ≥0.70. Patients meeting this definition had a 45 years median age and were vulnerable to heart failure, pneumonia, and mortality of all-cause related with those without obstruction of airflow [73]. In an integrated analysis of four US population-based cohorts (mean age 62.8 years), Bhatt et al (2019) evaluated multiple FEV_1/FVC thresholds, including LLN [74], and reported that 0.71 as best cutoff discriminated hospitalizations and mortality related to COPD. These findings supported the use of the fixed 0.70 threshold to identify at risk individuals of clinically significant COPD, although the debate between fixed ratio and LLN thresholds remained unresolved and appeared to be age dependent.

The 2001 GOLD report had introduced the category GOLD 0 for individuals with chronic respiratory symptoms (chronic cough, sputum production, mucus hypersecretion) but preserved FEV_1/FVC >0.70, considering them at risk of developing obstruction [75]. This classification was later removed as longitudinal studies showed that such individuals did not constitute the majority of those who progressed to COPD [76,77]. Nevertheless, smokers lacking obstruction but with persistent breathing symptoms continued to demonstrate substantial morbidity [78,79]. A related subgroup, termed preserved ratio impaired spirometry (PRISm), defined as FEV_1/FVC ≥0.70 but FEV_1 predicted<80%, gained increasing attention. In the Rotterdam Study, one out of three persons with PRISm turned to COPD within 4.5 years and both PRISm as well as GOLD stage 2-4 COPD were the causing factors of all-cause mortality [80]. These results emphasized the necessity for more research in identifying clinical, demographic and genetic factors that predispose people with PRISm to develop COPD and also in assessing if targeted interventions could change the course of the disease.

It was increasingly acknowledged that symptoms, exacerbations and chest CT abnormalities could improve the characterization of lung disease which is smoking-related even when spirometric obstruction is absent. In the SPIROMICS cohort, ever-smokers with preserved FEV_1/FVC (>0.70) but high symptom burden [COPD Assessment Test (CAT) ≥10] experienced more frequent exacerbations, were less capable of performing exercise and had airway thickening seen in CT, compared to those with fewer symptoms [81]. Importantly, 42% of these symptomatic patients were already on inhaled bronchodilators and 23% used inhaled corticosteroids, although they were not diagnosed with obstruction. This situation led to the start of a trial sponsored by the National Institutes of Health to assess the effectiveness of inhaled bronchodilators in symptomatic smokers without COPD confirmation by spirometry.

Chest CT has become more and more informative about subclinical smoking-related lung diseases [82]. Many ex-smokers with normal FEV_1/FVC (≥0.70) had radiographic changes, including emphysema and thickening of the airway wall, along with an increase in dyspnea, reduction in exercise capacity and worse respiratory health status as compared to never-smokers [83]. The results were suggestive of the fact that the definition based on guidelines that require airflow obstruction may not have completely covered the clinical spectrum of smoking related lung diseases. Moreover, advanced CT-based techniques like parametric response mapping (PRM) have made possible for the detection at very early stage. PRM used paired expiratory and inspiratory CT scans to classify lung tissue as normal, emphysematous or non-emphysematous areas with air trapping, termed functional small airways disease (fSAD) [84]. In smokers with a lifetime history of smoking and no obstruction or moderate-to-mild blockage, PRM fSAD was found to have a much

stronger association with the subsequent decrease in FEV_1 over five years than emphysema of PRM [85]. The pathologic confirmation in diseased lungs taken out at surgery showed that PRM fSAD was indicative of bronchiole loss, narrowing, thickening and obstruction at the terminal bronchiole level [86]. These results supported the hypothesis that the loss of small airways preceded emphysema and spirometric decline thus, making PRM fSAD a potential biomarker for early COPD.

Parallel studies explored the use of circulating biomarkers as diagnostic adjuncts. Biomarkers that could be changed, independently associated with outcomes and clinically actionable were regarded as the best candidates [87]. One of the main predictors of hospitalizations along with mortality, C-reactive protein (CRP), was found to be strongly independent of lung function and it was used to guide antibiotic administration during exacerbations [88]. High fibrinogen levels were linked with severe exacerbations, hospitalizations and death [89]. Blood eosinophils were associated with both the risk of exacerbation and the response to corticosteroids [90,91]. The soluble receptor for advanced glycation end products (sRAGE) gained attention due to its mechanistic link with emphysema development [92]. Large prospective cohorts were underway to assess the clinical use of these biomarkers.

Taken together, these results emphasized the need to integrate spirometry, clinical symptoms, imaging and biomarkers into diagnostic frameworks. Here, the COPD Gene investigators, among others, suggested new diagnostic categories reflecting reality more accurately by including exposure history, symptoms, CT imaging and spirometry, thus, they stratified patients as No COPD, Possible COPD, Probable COPD and Definite COPD [93]. Accelerating diagnostic certainty correlated with steeper lung function decline (>350 mL over five years) and higher all-cause mortality. However, the feasibility of applying such multidimensional criteria in primary care or resource limited settings where, spirometry and CT imaging were often unavailable—remained uncertain. Moreover, COPD gene participants had heavier smoking histories and prevalence of obstruction at higher rate than the community, limiting generalizability. Population-based studies were therefore required in future to determine the broader utility of these revised criteria and to clarify the predictive value of specific symptoms and imaging features.

Table 1: Diagnostic Tests Used in COPD

Diagnostic Test	Purpose / Key Findings
Spirometry (Post-Bronchodilator)	Gold standard for diagnosis; confirms persistent airflow obstruction defined as $FEV_1/FVC < 0.70$ (or below LLN). Assesses severity and progression.
Peak Expiratory Flow (with CAPTURE Questionnaire)	Used in case-finding to identify at-risk individuals in primary care before confirmatory spirometry.
Chest CT Scan	Detects subclinical lung disease, emphysema, and airway wall thickening even in absence of spirometric obstruction.
Parametric Response Mapping (PRM)	Advanced CT-based tool identifying functional small airways disease (fSAD) an early marker of COPD progression.
Blood Biomarkers	C-reactive protein (CRP): Predicts hospitalization and mortality. Fibrinogen: Associated with severe exacerbations. Blood eosinophils: Indicate corticosteroid responsiveness. sRAGE: Linked to emphysema development.
Questionnaires / Clinical Tools	CAPTURE: COPD screening tool for primary care. COPD Assessment Test (CAT): Assesses symptom burden and severity.
Imaging-based Lung Evaluation	Identifies early structural changes (emphysema, airway loss) and supports COPD diagnosis when spirometry is inconclusive.

Treatment

Pharmacotherapy

In the current years various clinical trials were conducted to evaluate the inhaler therapies efficacy in reducing exacerbation rates among patients with COPD. The FLAME (Effect of Indacaterol-Glycopyrronium versus Fluticasone-Salmeterol on COPD Exacerbations) trial demonstrated that a

combination of LABA/LAMA (indacaterol–glycopyrronium) was additionally efficacious than a combination of LABA/ICS (salmeterol–fluticasone) in exacerbations prevention [94]. Similarly, the IMPACT (Informing the Pathway of COPD Treatment) trial compared triple inhaler therapy - umeclidinium (LAMA), vilanterol (LABA) and fluticasone furoate (ICS) - with either umeclidinium-vilanterol or fluticasone furoate-vilanterol in patients experiencing the exacerbations regularly and obstruction of airflow at moderate [95]. Triple therapy considerably reduced the moderate or severe exacerbations rate compared with either dual regimen. Unlike the FLAME trial, IMPACT demonstrated considerable reduction of exacerbation with LABA/ICS compared with LAMA/LABA. This difference was partly attributed to study design, as FLAME included a 4-week run-in with tiotropium, certainly patients are selected who were stable without ICS. At that time, GOLD recommendations for group D patients (high symptom burden and exacerbation risk) included LAMA, LAMA/LABA, or LABA/ICS as initial choice, with triple therapy reserved for exacerbations persistently [96]. Notably, mortality of all-cause also reduced with triple therapy when compared with LAMA/LABA [97].

Evidence guiding step-down of ICS therapy in patients lacking regular exacerbations was limited. The SUNSET (Study to Understand the Safety and Efficacy of ICS Withdrawal from Triple Therapy in COPD) trial evaluated stable patients on triple therapy for long-term with ≤1 exacerbation in the preceding year. Withdrawal of ICS led to a modest but notable FEV1 (26 ml) decline, though exacerbation rates remained unchanged. Importantly, patients with elevated eosinophil counts (≥300 cells/µl) at baseline experienced greater lung function decline and more exacerbations after ICS withdrawal [98]. Findings from the WISDOM trial aligned with this view, as higher eosinophil counts were associated with increased exacerbations after ICS withdrawal [99]. A secondary analysis of the IMPACT trial, where eosinophils were considered a continuous variable, revealed that there was no difference in treatment effect between triple therapy and LAMA/LABA at eosinophil counts <100 cells/µl, while at higher counts, the benefit of ICS increased gradually [100]. These findings led to the 2019 GOLD recommendations that use blood eosinophil levels in conjunction with exacerbation history and symptom burden to determine treatment, thus representing a move towards precision-based COPD management [101].

As eosinophilia was linked to the risk of exacerbations, biologic therapies targeting type 2 inflammation were considered. Clinical trials of interleukin-5 monoclonal antibodies, like benralizumab and mepolizumab which are generally recommended for eosinophilic asthma [102] showed inconsistent results, with only one study reporting a decrease in the rate of exacerbations [103]. There were large trials underway to establish their potential in COPD management further.

Oral pharmacotherapies were considered in patients who continued to exacerbate in spite of inhaler therapy maximally, particularly in those with eosinophil counts (<100 cells/µl) at low who derived limited benefit from ICS. Azithromycin prophylaxis reduced exacerbations in high-risk patients [104], though benefits were less evident in smokers, supporting its primary use in ex-smokers [105]. Complications included prolongation of QTc, hearing loss, and the potential for antibiotic resistance, warranting close monitoring. Roflumilast, which is a phosphodiesterase-4 inhibitor, reduced exacerbation frequency of recurrent exacerbations in patients, predicted FEV1 <50%, and phenotype of chronic bronchitis and was recommended in this subgroup [106].

Beyond pharmacologic bronchodilation, skeletal muscle loss was recognized as a contributor to exacerbation risk and mortality [107-109]. A placebo-controlled trial of bimagrumab, is a monoclonal antibody targeting type II activin receptors, demonstrated increased muscle volume of thigh and lean body mass for up to 24 weeks in sarcopenic COPD patients [110]. However, improvements in physical function were not observed, leaving uncertainty about whether mass of the muscle gains could interpret into improved outcomes of respiration.

Table 2: Pharmacological Agents Used in COPD

Drug Name	Pharmacologic Class	Usual Dosage Range / Formulation	Major Adverse Drug Reactions (ADRs)
Tiotropium	Long-Acting Muscarinic Antagonist (LAMA)	Inhalation: 18 µg once daily (Handi Haler) or 5 µg once	Dry mouth, constipation, urinary retention, glaucoma risk

		daily (Respimat)	
Glycopyrronium bromide	LAMA	Inhalation: 50 µg once daily	Dry mouth, throat irritation, tachycardia
Umeclidinium	LAMA	Inhalation: 62.5 µg once daily	Headache, cough, dry mouth
Indacaterol	Long-Acting β_2-Agonist (LABA)	Inhalation: 150–300 µg once daily	Tremor, palpitations, headache, hypokalemia
Vilanterol	LABA	Fixed combination inhaler: 25 µg once daily (with LAMA or ICS)	Nervousness, tachycardia, muscle cramps
Salmeterol	LABA	Inhalation: 50 µg twice daily	Tremor, insomnia, hypokalemia
Formoterol	LABA	Inhalation: 12–24 µg twice daily	Palpitations, dizziness, tremor
Fluticasone propionate / furoate	Inhaled Corticosteroid (ICS)	Inhalation: 100–250 µg twice daily (propionate); 100–200 µg once daily (furoate)	Oral candidiasis, hoarseness, pneumonia, adrenal suppression (high doses)
Budesonide	ICS	Inhalation: 200–400 µg twice daily	Oral thrush, cough, dysphonia
Indacaterol + Glycopyrronium (FLAME Trial)	LABA/LAMA Combination	Once daily (fixed-dose inhaler)	Dry mouth, headache, tremor
Umeclidinium + Vilanterol (Anoro Ellipta)	LAMA/LABA Combination	Once daily inhalation	Nasopharyngitis, cough, muscle cramps
Fluticasone furoate + Vilanterol + Umeclidinium (Trelegy Ellipta)	Triple Therapy (ICS/LABA/LAMA)	Once daily inhalation	Pneumonia, oral thrush, headache, tremor
Roflumilast	Phosphodiesterase-4 (PDE-4) Inhibitor	Oral: 500 µg once daily	Diarrhea, weight loss, nausea, insomnia, depression
Azithromycin	Macrolide Antibiotic (Anti-inflammatory/Prophylactic)	Oral: 250 mg daily or 500 mg three times/week	QT prolongation, hearing loss, GI upset, bacterial resistance
Mepolizumab	Anti–IL-5 Monoclonal Antibody (Biologic)	Subcutaneous: 100 mg every 4 weeks	Headache, injection site reaction, hypersensitivity

Benralizumab	Anti–IL-5Rα Monoclonal Antibody	Subcutaneous: 30 mg every 4 weeks for 3 doses, then every 8 weeks	Fever, rash, antibody development
Bimagrumab	Anti–Activin Type II Receptor Monoclonal Antibody	Intravenous: 10 mg/kg every 4 weeks (trial-based)	Diarrhea, muscle pain, headache, nausea
Theophylline *(Second line drug)*	Methylxanthine (Bronchodilator)	Oral: 100–400 mg/day, adjusted for serum levels (5–15 µg/mL)	Nausea, tremor, arrhythmia, seizures, insomnia

Non-Pharmacological Treatment

Pulmonary Rehabilitation (PR)

PR was established as a complete, longitudinal mediation that incorporated physical activity, education and strength training to upgrade the psychological and physical well-being of the COPD patients. It was consistently appeared to improve the functional capacity, increase health-related quality of life and reduction in hospitalizations. In spite of its proven efficacy, PR remained underused, largely due to limited access and low awareness among providers, patients and payers [111,112]. A large Medicare beneficiaries cohort study hospitalized for COPD manifested that within 90 days of discharge with PR initiation was correlated with reduction in fatality of all-cause at twelve months compared with no or delayed initiation [113].

Reduction of Lung Volume

Lung volume reduction surgery (LVRS) was one of the few surgical options for COPD, based on the principle that resection of emphysematous lung tissue permitted expansion of healthier lung regions. LVRS conferred a benefit of mortality in patients with upper-lobe–predominant emphysema and poor tolerance to exercise in spite of prior PR [114,115]. Nevertheless, it was infrequently performed due to eligibility restrictions, physician concerns about risks and accreditation requirements [116,117]. Endobronchial valves (EBVs) provided a less invasive alternative for patients ineligible for LVRS. The LIBERATE and EMPROVE randomized controlled trials evaluated EBVs in patients with airflow obstruction at severe, hyperinflation, heterogeneous emphysema and little or no collateral ventilation [118,119]. Both trials demonstrated significant improvements in FEV1, residual volume, respiratory health status and six-minute walking distance at 6 and 12 months, leading to FDA approval for selected patients.

Emerging Interventions

Targeted lung denervation (TLD) involved the use of bronchoscopic radiofrequency ablation to interrupt pulmonary parasympathetic nerve activity aimed at reducing broncho-constriction, mucus secretion and airway inflammation was the focus of investigation [120]. In a similar fashion, bronchial rheoplasty using pulsed electric fields for the ablation of mucus-producing cells demonstrated at the inception the reduction of goblet cell hyperplasia and the improvement of symptoms [121,122]. Nevertheless, both procedures require confirmation in large randomized trials.

Lung Transplantation

Advanced COPD treatment was still through lung transplantation, with COPD being the major worldwide and the second most common cause in the United States of lung transplantation [123]. The International Society for Heart and Lung Transplantation guidelines suggested referral of patients with a BODE index of 5-6, FEV1 <25% predicted, disease progression and severe gas exchange abnormalities. Timing remained a clinical challenge due to the usually long-term course of COPD and comparatively good survival in the intermediate term, as opposed to other types of advanced lung diseases [124].

Oxygen Therapy

Long-term oxygen therapy was perhaps the first treatment intervention that was proven to eventually bring about the survival of COPD patients. The Nocturnal Oxygen Therapy Trial (NOTT, 1980) showed that the use of oxygen continuously allowed patients to live longer those with severe hypoxemia at rest (PaO2 ≤55 mmHg or SpO2 ≤88%) or with PaO2 55-60 mmHg in the presence of pulmonary hypertension, polycythemia, or heart failure

complications [125]. On the other hand, the Long-Term Oxygen Treatment Trial (LOTT, 2016) showed that there was no benefit to survival or decrease of hospitalizations in patients with moderate hypoxemia at rest and those with isolated exertional desaturation, thus pointing to the necessity of having more stringent criteria for long-term oxygen use [126].

Chronic Non-invasive Ventilation (NIV)

NIV was well established as a life-saving therapy during acute COPD exacerbations with hypercapnic respiratory failure. Its role in stable outpatients with chronic hypercapnia was less clear [127]. One randomized trial involving patients with persistent hypercapnia (PaCO2 >53 mmHg) after a hospitalization for acute hypercapnic respiratory failure showed that home non-invasive ventilation plus oxygen improved outcomes compared with oxygen alone [128]. Reviews of stable COPD populations highlighted that benefits in quality of life and survival were seen only when NIV effectively reduced hypercapnia, with adherence being a major limiting factor [129].

Table 3: Non-Pharmacological Management of COPD

Intervention	Mechanism / Description	Key Evidence / Study	Clinical Benefits / Outcomes	Limitations / Considerations
Pulmonary Rehabilitation (PR)	Comprehensive program combining exercise training, education, and psychological support to improve physical and mental well-being.	Multiple RCTs and cohort studies; large Medicare cohort showed mortality reduction with PR within 90 days of discharge.	↑ Exercise capacity, ↑ quality of life, ↓ dyspnea, ↓ hospitalizations, ↓ 1-year mortality.	Underutilized due to low awareness, limited availability, and lack of referrals.
Lung Volume Reduction Surgery (LVRS)	Surgical removal of diseased emphysematous lung to allow expansion of healthier tissue and improve lung mechanics.	NETT trial and follow-up studies.	Mortality benefit in upper-lobe–predominant emphysema with poor exercise tolerance despite PR.	Limited eligibility, surgical risk, high cost, and need for specialized centers.
Endobronchial Valves (EBVs)	Bronchoscopic placement of one-way valves to achieve targeted lung volume reduction without surgery.	LIBERATE and EMPROVE RCTs.	↑ FEV_1, ↓ residual volume, ↑ exercise capacity, ↑ quality of life (6–12 months).	Only for selected patients with heterogeneous emphysema and minimal collateral ventilation.
Targeted Lung Denervation (TLD)	Bronchoscopic radiofrequency ablation to disrupt parasympathetic nerve input → reduces bronchoc	Early phase clinical trials.	Improved symptoms and airflow; potential reduction in exacerbations.	Experimental—needs validation in large RCTs.

	onstriction, mucus, and inflammation.			
Bronchial Rheoplasty	Pulsed electric field ablation to reduce mucus-producing goblet cells and airway remodeling.	Early clinical studies.	↓ Goblet cell hyperplasia, ↓ mucus production, symptom improvement.	Preliminary data; larger trials needed.
Lung Transplantation	Replacement of one or both lungs in end-stage COPD.	ISHLT Guidelines	Improved survival and quality of life in advanced COPD with FEV_1 <25%, BODE ≥5, severe gas exchange abnormalities.	Timing challenging; lifelong immunosuppression and risk of rejection/ infection.
Long-Term Oxygen Therapy (LTOT)	Continuous oxygen administration to correct chronic hypoxemia (PaO_2 ≤55 mmHg or SpO_2 ≤88%).	NOTT (1980): Improved survival. LOTT (2016): No benefit in	↓ Mortality in severe hypoxemia; improves exercise tolerance and cognitive	No benefit in moderate or exertional hypoxemia; adherence and equipment limitations.
		moderate hypoxemia.	function.	
Chronic Non-Invasive Ventilation (NIV)	Positive pressure ventilation via mask to reduce chronic hypercapnia and improve gas exchange.	RCT in post-acute hypercapnic COPD ($PaCO_2$ >53 mmHg).	↓ Mortality and readmissions; ↑ quality of life if hypercapnia reduced effectively.	Requires strict adherence; benefits only in hypercapnic patients.

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