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IN SEARCH OF NOVEL PHARMACOLOGICAL THERAPIES FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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ABSTRACT

Background: Chronic Obstructive Pulmonary Disease (COPD) remains a significant global health challenge. Its progressive nature and variability in symptoms—often resulting in exacerbations and hospitalizations—contribute to a lower quality of life, reduced physical activity, and impaired psychological well-being. Despite advances in treatment, tailored to symptom severity, disease progression continues to be a major challenge. Current pharmacological therapeutic strategies primarily involve bronchodilators and inhaled corticosteroids. However, there is a persistent need for more effective and targeted interventions.

Methods: A comprehensive literature review was conducted for English-language publications using databases such as PubMed. Meta-analyses, systematic literature reviews, randomised controlled trials, cohort studies, case-control studies and cross-sectional studies were included. Articles published after 2016 were reviewed; in the case of older articles, only those that made a significant new contribution to the field were taken into consideration. Methodological rigor and limitations of included studies were critically discussed.

Results: Several therapies have demonstrated clinically relevant effects in late-stage trials, leading to recent regulatory approvals in the United States: ensifentrine in 2024 as a dual PDE3/PDE4 inhibitor for maintenance treatment of COPD, dupilumab in 2024 as maintenance biologic therapy for COPD with an eosinophilic phenotype, and mepolizumab in 2025 as maintenance treatment for inadequately controlled eosinophilic COPD. Other investigational agents, including IL-33 pathway inhibitors such as itepekimab and tozorakimab, have produced mixed or emerging Phase III results.

Conclusions: This review examines recent advancements in COPD therapy, with an emphasis on ongoing research and emerging pharmacological candidates that hold promise for improving patient outcomes.

KEYWORDS

Chronic Obstructive Pulmonary Disease, Pulmonology, Pharmacological Treatment, Personalized Therapy, Biological Treatment

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1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a chronic lung disease that remains a major challenge for global health. It causes a number of respiratory symptoms, most characteristically include cough, shortness of breath, sputum production. In addition, it is known for its progressive nature and variability of symptoms, which can cause exacerbations that require hospitalization. COPD negatively affects a number of aspects of a patient's life, including reduction in quality of life, physical activity levels, psychological functioning, and sleep deprivation (Miravitless et al., 2017). Macroeconomic losses due to COPD are estimated in the trillions of dollars, and the economic costs are borne by all countries, especially those with lower incomes (Chen et al., 2023). Due to the many studies conducted on different groups and at different times, it is not straightforward to state the exact prevalence of COPD in the population. It can be assumed that it is approximately 10% (Al Wachami et al., 2024; Adeloye et al., 2022). In addition, the number of COPD cases, deaths and disability-adjusted life years (DALYs) increased significantly worldwide in the last 30-year period (Li et al., 2023).

The pathomechanism of COPD is complex. There is observed an airway luminal cellular inflammation and fibrosis and obliteration of the small airways, as well as remodelling changes (Walters et al., 2021). Well-established risk factors include primarily cigarette smoking (also the increasing popularity of electronic cigarettes), resulting in inflammation through increased production of cytokines, which subsequently recruits neutrophils, macrophages, and dendritic cells and secondly, the environmental pollution (Zhang et al., 2021). In recent years, attention has focused on potentially new factors such as genetic changes in the extracellular matrix of the lung, and age- or sex-related changes (Brandsma et al., 2020).

The main goal of treatment is to relieve symptoms and prevent exacerbations. Pharmacological treatment according to the 2024 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines is based on the use of medications by distinguishing 3 groups of patients with an assessment of symptom severity and exacerbation risk (Groups A, B, E) (Venkatesan, 2024). The primary treatment in group A is the use of a bronchodilator (either a short- or long-acting), while in group B it is a combination of Long-Acting Beta-2 Agonist (LABA) and Long-Acting Muscarinic Antagonist (LAMA). Group E also has a two-drug regimen of LABA+LAMA, and an inhaled corticosteroid (ICS) can be added if blood eosinophils are ≥ 300 cells/ μ L (Venkatesan, 2024). Because of the progressive course of the disease, exacerbations become a cause for concern, which may be triggered by respiratory infections or environmental factors, potentially resulting in hospitalization (Vogelmeier et al., 2020). This highlights the need not only to optimize current treatment strategies but also to explore novel therapeutic options.

The main purpose of this review is to acquaint the reader with available as well as ongoing trials of advanced drug therapies for COPD.

2. Material and methods

The database search was based on articles in the following databases: PubMed, Scopus, Web of Science, Google Scholar, National Library of Medicine. To maintain the validity of the information cited, the publication date of the articles searched was up to 10 years. Meta-analyses, systematic literature reviews, randomised controlled trials, cohort studies, case-control studies, cross-sectional studies and ongoing clinical trials (data obtained from ClinicalTrials.gov) were included. In the case of older articles, only those that made a significant new contribution to the field were taken into consideration. Case reports were excluded. The studies cited in this article were those conducted on both humans and animal models in accordance with the principles of bioethics. The screening process involved independent review of titles and abstracts by at least two authors. Full-text articles were retrieved for those studies deemed potentially eligible. Only abstracts and articles in English were considered. Disagreements were resolved by consensus. Approval from the Bioethics Committee was not required.

3. Current therapeutic options for patients with COPD

The classes of medications indicated for the management of both stable COPD and acute exacerbations are summarized in Table 1. The data presented are based on three guidelines: 2024 Global Initiative for Chronic Obstructive Lung Disease (GOLD) (Venkatesan, 2024), 2023 Canadian Thoracic Society (CTS) (Bourbeau et al., 2023), and 2020 American Thoracic Society (ATS) (Nici et al., 2020).

Table 1. Summary of pharmacological management of Chronic Obstructive Pulmonary Disease According to GOLD (2024), CTS (2023), and ATS (2020)

	Bro	ICS	OCS	PDE4	Anti	Muco	AA	Stat	A-1ATT	ASV	Vaso	Opi
GOLD (2024)	R	R	C	C	C	C	C	NR	C	NR	NR	C
CTS (2023)	R	R	C	C	C	C		NR	C			C
ATS (2020)	R	R	C		C							C

Abbreviations:

Bro – bronchodilators; ICS – inhaled corticosteroids; OCS – oral glucocorticoids; PDE4 – PDE4 inhibitors; Anti – antibiotics; Muco – mucolytics; AA – antioxidant agents; Stat – statins; A-1ATT – alpha-1 antitrypsin augmentation therapy; ASV – antitussives; Vaso – vasodilators; Opi – opioids; PHT – pulmonary hypertension therapy; R – recommended; C – consider (use in selected cases); NR – not recommended

4. Novel pharmacological therapies

4.1 Phosphodiesterases

Autoimmune mechanisms, including self-sustaining inflammation, population susceptibility, acute exacerbations and insensitivity to ICS treatment, are increasingly being discussed in the pathogenesis of COPD as a chronic disease (Dong et al., 2024). One potential anti-inflammatory mechanism involves the inhibition of phosphodiesterases 4 and 3 (PDE4 and PDE3), which hydrolyze cyclic adenosine monophosphate (cAMP) and both cAMP and cyclic guanosine monophosphate (cGMP), respectively. These ubiquitous second messengers play essential roles in regulating numerous cellular functions in pulmonary physiology and pathology (Schmidt et al., 2020). A normal concentration of cAMP suppresses key inflammatory responses. Elevated PDE levels cause cAMP to be hydrolyzed into an inactive form (AMP), which reduces the amount of cAMP and triggers an inflammatory process (Nourian et al., 2023). Both PDE3 and PDE4 are found in various components of the respiratory system (Zuo et al., 2019). Reports have shown that expression levels of PDE4 isoforms were higher in patients with COPD compared to individuals without the disease (Zuo et al., 2019).

In previous years, PDE4 inhibitors - tofomilast and cilomilast - were researched. The development of tofomilast was discontinued due to lack of efficacy in Phase II clinical trials (Facchinetti et al., 2021). Regarding cilomilast, Phase II and early Phase III trials were promising, but subsequent Phase III trials did not confirm its efficacy, despite its good safety profile (Rennard et al., 2008). Nevertheless, research into drugs targeting this mechanism has continued, leading to some very important results. Roflumilast, a PDE4 inhibitor, is used in clinical practice for patients who continue to experience exacerbations despite treatment with LABA, LAMA, and ICS. Clinical studies have demonstrated that roflumilast improves forced expiratory volume in one second (FEV₁), significantly reduces exacerbation rates, and decreases the number of inflammatory cells and cytokines in the airways (Shen et al., 2018). On the other hand it was associated with a variety of adverse effects including diarrhea and weight loss (Shen et al., 2018). It is worth mentioning that a new dual PDE3/PDE4 inhibitor, ensifentrine, has recently emerged as a therapeutic option for COPD. In June 2024, U.S. Food and Drug Administration (U.S. FDA) approved the use of ensifentrine for the maintenance treatment of COPD in adult patients by oral inhalation using a standard jet nebulizer with a mouthpiece (U.S. Food and Drug Administration, 2024). Tanimilast, an inhaled PDE4 inhibitor, was evaluated in a Phase III clinical development programme for COPD, including the PILASTER (NCT04636801) and PILLAR (NCT04636814) trials. However, these studies were subsequently terminated for sponsor-related strategic reasons.

4.2. Biologics

Some patients with COPD exhibit a type 2 inflammatory phenotype (Rabe et al., 2023). This observation has prompted efforts to identify personalized, targeted therapies aimed at pro-inflammatory interleukins—specifically IL-4, IL-5, and IL-13—as well as epithelial-derived alarmins such as thymic stromal lymphopoietin (TSLP) and interleukin-33 (IL-33), which are already established therapeutic targets in asthma (Rabe et al., 2023). Other pro-inflammatory interleukins, IL-6 and IL-8, are also under investigation in the context of COPD. However, no consistent or clinically significant associations between their circulating levels and disease outcomes have been demonstrated to date, and their precise roles remain insufficiently understood, necessitating further research (Fermont et al., 2019). Continuing with the investigation of pro-inflammatory pathways, a further point of intervention could be the blocking of pro-inflammatory IL-1, which shows increased expression and release in patients with respiratory diseases such as COPD or asthma (Osei et al., 2020). Fully human monoclonal antibody (MEDI8968) targeting interleukin-1 receptor type 1 (IL-1R1) has been evaluated. In a Phase II clinical trial, this agent was well tolerated but did not produce statistically significant improvements in exacerbation rate, pulmonary function, or health-related quality of life when compared with placebo (Calverley et al., 2017).

4.2.1 Alarmins

Alarmins are released as a result of degranulation, cell injury or death or in response to immune induction. The epithelial-derived alarmin cytokines IL-33 and TSLP can influence both type 1 and type 2 inflammation in COPD (Celli et al., 2025). Astegolimab, a selective monoclonal antibody for ST2 receptor of epithelial-derived IL-33 is currently being investigated in COPD. Compared to placebo, no alteration in exacerbation rate was observed. However, the Saint George's Respiratory Questionnaire for COPD (SGRQ-C) was significantly lower in astegolimab group versus placebo group (Yousuf et al., 2022). Another human monoclonal antibody targeting interleukin 33 and ST2 is tozoracimab, which in a randomized Phase I study was well tolerated and significantly reduced serum levels of pro-inflammatory IL-5 and IL-13 in COPD patients compared to placebo (Reid et al., 2024). Itepekimab is also a monoclonal antibody targeting IL-33. In a Phase 2a trial, itepekimab reduced exacerbation rates and improved lung function, measured by FEV₁, compared with placebo, with benefits observed mainly in former smokers rather than current smokers (Rabe et al., 2021). The AERIFY Phase III programme was subsequently designed to evaluate itepekimab in former smokers with moderate-to-severe COPD (Rabe et al., 2024). Interestingly, these results were only observed in a subgroup of former smokers; current smokers did not have these benefits. Another alarmin is TSLP, which is targeted by tezepelumab. In a Phase 2a trial, although it showed a good safety profile, there was no statistically significant reduction in the number of exacerbations compared to placebo (Singh et al., 2025).

4.2.2. Interleukins -4, -5,-13

Mepolizumab, a humanized monoclonal antibody targeting interleukin-5 (IL-5), is another biologic agent evaluated in the treatment of COPD. Compared with placebo, mepolizumab significantly reduced the frequency of exacerbations, with the greatest benefit observed in patients with blood eosinophil counts ≥ 300 cells/ μ L (Pavord et al., 2021). In the Phase III MATINEE trial, mepolizumab added to background triple inhaled therapy reduced the annualized rate of moderate or severe exacerbations in patients with COPD and an eosinophilic phenotype (Sciurba et al., 2025). In May 2025, the U.S. FDA-approved label for mepolizumab was updated to include its use as an add-on maintenance treatment for adult patients with inadequately controlled COPD and an eosinophilic phenotype (U.S. Food and Drug Administration, 2025). Considering the pro-inflammatory IL-5, it is worth noting the study on benralizumab, an antibody directed against its alpha receptor. Although it has demonstrated a good safety profile, the annual rates of COPD exacerbations associated with benralizumab were not significantly lower than those associated with placebo (Criner et al., 2019).

Research has also focused on dupilumab, a monoclonal antibody that targets interleukin-4 (IL-4) and interleukin-13 (IL-13). In the Bhatt et al. study, as with the cited research on mepolizumab, patients with blood eosinophil counts ≥ 300 cells/ μ L had a statistically significant lower rate of moderate or severe exacerbations and a higher increase in FEV₁ compared to placebo (Bhatt et al., 2024). In September 2024, U.S. FDA has approved subcutaneously administered dupilumab as maintenance treatment of adult patients with inadequately controlled COPD and an eosinophilic phenotype. It is noteworthy that it is not indicated for the relief of acute bronchospasm (U.S. Food and Drug Administration, 2024).

4.3. Vitamin C and D

The role of vitamin C is to prevent oxidative damage to biomolecules by directly scavenging free radicals, being a cofactor for many enzymes that catalyse important reactions, lowering the levels of inflammatory mediators and improving microcirculatory blood flow (Ghalibaf et al., 2023). Its potential role in the management of COPD has been explored in both experimental and clinical contexts (Ghalibaf et al., 2023). A recent cross-sectional study shows that daily vitamin C intake of 50.1–135.6 mg is negatively correlated with the risk of COPD (Tao et al., 2025). Regarding COPD patients, a meta-analysis results showed that vitamin C supplementation (≥ 400 mg/day) can significantly improve the %FEV₁ and FEV₁/FVC (forced vital capacity) (Lei et al., 2022).

Vitamin D deficiency was observed in patients with COPD in spite of regular exposure to sunlight. Notably, amongst subjects with COPD, vitamin D deficient subjects were three times more likely to have exacerbations in the previous year as compared to COPD subjects without vitamin D deficiency (Lokesh et al., 2021). Another study demonstrated that vitamin D deficiency is associated with respiratory symptoms and airway wall thickening (observed in CT scans) in smokers with and without COPD (Ghosh et al., 2020). This raises the question of where these deficits originate and how they may affect the course of COPD. The results of meta-analyses on the use of vitamin D in patients with COPD are divergent. Data from Williamson et al. study show that little or no effect of administering cholecalciferol (vitamin D3) was observed on the rate of moderate or severe exacerbations, change of lung volumes and difference to mortality or quality of life (Williamson et al., 2024). In contrast, meta-analyses by Wang et al. and Zhu et al. showed that such supplementation can improve pulmonary function, SGRQ scores, 6-minute walk distance (6MWD) and reduce acute exacerbation, sputum volume and COPD assessment test (CAT) score (Wang et al., 2022; Zhu et al., 2016).

4.4. Probiotics

Concomitant gastrointestinal symptoms in patients with COPD, including intestinal diseases, require further research focused on the gastrointestinal tract (Wang et al., 2023). Studies have demonstrated that the gut microbiome of COPD patients varied from that of healthy controls and was characterised by a distinct overall microbial diversity and composition (Li et al., 2021; Bowerman et al., 2020). Similarly, dysbiosis is also observed within the lung microbiota, leading to altered metabolite profiles, increased production of proinflammatory cytokines, and impaired immune responses (Qu et al., 2022). This leads to potential therapeutic considerations for another axis of the microbiota, formed from the lungs and gastrointestinal tract. A meta-analysis showed that multi-probiotic supplement significantly improved %FEV₁ in stable COPD patients and reduced inflammation by substantially modulating inflammatory cytokine levels in animal models (Su et al., 2024). A clinical trial is currently ongoing on probiotic supplementation in pulmonary rehabilitation in patients with COPD (NCT06717659).

4.5. Vasodilators

A significant proportion of patients with chronic obstructive pulmonary disease (COPD) are either current or former smokers, a factor that not only contributes to the progression of pulmonary disease but is also strongly associated with an increased risk of cardiovascular comorbidities. This overlap between pulmonary and cardiovascular pathology has led to growing interest in the potential cardiopulmonary benefits of certain drug classes in patients with COPD (Gulea et al., 2021; Tejawani et al., 2021). A meta-analysis conducted by Han et al. assessed the efficacy of eight different groups of vasodilators—namely angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), nitrates, phosphodiesterase-5 (PDE-5) inhibitors, nitric oxide (NO) donors, prostacyclins, and endothelin receptor antagonists—in the context of COPD management (Han et al., 2024). It has been observed that these drugs may have some beneficial effects on several levels, ranging from improving gas-blood exchange function to improving quality of life. However, the therapeutic effects of long-term application of vasodilators in the treatment of COPD remain unclear.

4.6. p38 MAPK inhibitors

p38 mitogen-activated protein kinase (MAPK) is activated through a kinase cascade triggered by extracellular inflammatory stimuli (Pelaia et al., 2021). It contributes to the pathophysiology of COPD by coordinating intercellular cross-talk between CD8⁺ T lymphocytes and alveolar macrophages. Therefore, inhibition of this pathway is being considered as a potential therapeutic strategy. However, the results of clinical studies remain inconsistent. Acumapimod, a selective oral p38 inhibitor, was well tolerated and was demonstrated to improve FEV₁ compared to placebo (Strâmbu et al., 2019). On the other hand, two studies on Losmapimod, also a p38 MAPK inhibitor, demonstrated that it did not cause an improvement in exercise tolerance or lung function as well as no effect on arterial inflammation and endothelial function, despite being well-tolerated in COPD patients (Watz et al., 2014; Fisk et al., 2018). RV568, an inhibitor of p38 mitogen-activated protein kinase- α and - γ as well as SRC family kinases, showed potent anti-inflammatory effects in cell and animal models relevant to COPD. Moreover, in a small clinical trial, it exhibited a favorable safety profile and improved FEV₁ and residual volume compared to placebo (Charron et al., 2017).

4.7. CFTR regulation

The cystic fibrosis transmembrane conductance regulator (CFTR) is a chloride channel whose role in the pathogenesis of COPD is receiving increasing attention. CFTR is primarily responsible for maintaining epithelial surface hydration and regulating luminal pH in epithelial cells, but it is also expressed in non-epithelial cells, where it influences the function of immune cells, fibroblasts, keratinocytes, and endothelial cells (Mall et al., 2023). In patients with COPD who do not have cystic fibrosis, CFTR dysfunction may occur through mechanisms other than inherited mutations—the most well-documented of which is cigarette smoking (Mall et al., 2023). The first study of the CFTR potentiator, icentricaftor (QBW251), shows that although the primary endpoint of an increase in FEV₁ was not achieved, it suggests potential benefits in including symptoms, quality of life outcomes, and fibrinogen concentrations for patients with COPD and chronic bronchitis (Martinez et al., 2023). In contrast, the second study observed an improvement in FEV₁, with the same dose of icentricaftor as in the previous study, 300 mg orally twice daily (Rowe et al., 2020). In another clinical trial in COPD patients of CFTR potentiators, ivacaftor was safe and well tolerated, but did not improve sweat chloride, whole lung mucociliary clearance, lung function or respiratory symptoms (Vijaykumar et al., 2025).

5. Conclusions

In this review, a number of new drug families involving different mechanisms of action have been presented. Particular emphasis was placed on recently approved therapeutic options, including ensifentrine and biologic therapies targeting type 2 inflammation, as these offer promising add-on or maintenance treatment strategies for selected patients with COPD. Long-term studies may determine whether these therapies will remain purely maintenance-oriented or whether they hold the potential to modify disease progression or even suppress it. However, this remains a subject for future investigation, as does the ongoing search for new therapeutic strategies targeting exacerbations. We acknowledge that not all trials of novel therapies were included; our intention was to focus on studies that demonstrate at least some degree of clinical, rather than purely experimental, efficacy. We hope that this review will encourage clinicians and researchers to explore further the therapeutic potential of COPD—a disease that remains one of the greatest challenges not only in respiratory medicine but also in the broader context of chronic disease management.

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