Review

Phosphodiesterase Inhibition as a Therapeutic Strategy for Chronic Obstructive Pulmonary Disease: Where We Have Been and What Lies Ahead

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***Running Head*: PDE Inhibition for COPD Therapy**

***Keywords*:** COPD; quality of life; standard of care; phosphodiesterase; PDE4 inhibitors

***Abbreviations*:** COPD, chronic obstructive pulmonary disease; PDE, phosphodiesterase; TNF, tumor necrosis factor; IL-1 β, interleukin 1β; GM-CSF, granulocyte-macrophage colony-stimulating factor; C-X-C, chemokine; IL-8, ligand 8; TGF-β, transforming growth factor β; GOLD, Global Initiative for Chronic Obstructive Lung Disease; LABA, long-acting β_2 agonist; LAMA, long-acting muscarinic antagonist; ICS, inhaled corticosteroids; pMDI, pressurized metered-dose inhaler; DPI, dry powder inhaler; SMI, soft mist inhaler; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; CFTR, cystic fibrosis transmembrane conductance regulator; FEV_1, forced expiratory volume in 1 second; FDA, US Food and Drug Administration; E-RS, Evaluating Respiratory Symptoms in COPD; SGRQ-C, St. George's Respiratory Questionnaire – COPD Specific; TDI, Transition Dyspnea Index; ENHANCE, Ensifentrine as a Novel Inhaled Nebulized COPD Therapy; $AUC_{0\text{-}12h}$, area under the concentration time curve from 0 to 12 hours; AE, adverse event; BID, twice daily.

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Abstract

Chronic obstructive pulmonary disease (COPD) is a highly prevalent inflammatory lung condition characterized by chronic respiratory symptoms and airflow obstruction that often lead to diminished quality of life. Non-pharmacologic management for patients with COPD involves smoking cessation and healthy lifestyle changes. Pharmacologic treatments include inhaled bronchodilators with or without the use of inhaled corticosteroids, which can be administered through inhalation or nebulization. In addition, oral medications including macrolide antibiotics and phosphodiesterase (PDE) 4 inhibitors can help reduce exacerbation risk. However, many of these medications provide suboptimal disease control, owing to limited efficacy, increased risk of adverse events with long-term use, or difficulty in administration technique. PDE3 plays an important role in maintaining smooth muscle function, and PDE4 plays a crucial role in the inflammatory response in airway smooth muscle. Direct molecular inhibition of PDE3 or PDE4 has been shown to provide benefit in COPD. Dual PDE3 and PDE4 inhibition may therefore have synergistic anti-inflammatory and bronchodilator effects. These results have been observed in clinical trials of nebulized ensifentrine, a novel, dual-action PDE3 and PDE4 inhibitor that is the first in its class to be approved by the US Food and Drug Administration for maintenance treatment of COPD in adult patients. In this review, we explore the pathophysiologic mechanisms of COPD, describe current paradigms and methods of drug delivery for the treatment of the disease, and illustrate how dual inhibition of PDE3 and PDE4 may provide additional benefit to current standard-of-care regimens.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous lung condition characterized by respiratory symptoms that cause persistent, progressive airflow obstruction [1]. As a leading cause of morbidity and mortality both in the US and globally [1,2], COPD affects approximately 10.6% (480 million) of people worldwide, and its prevalence is projected to increase to a total of 592 million by 2050 [3]. In addition to a substantial symptom burden such as chronic coughing, dyspnea, and fatigue, many patients experience frequent exacerbations that affect their quality of life and lead to accelerated lung function decline and risk of death [1,4]. Furthermore, patients with COPD have a high prevalence of multimorbidities including cardiovascular, cerebrovascular, metabolic, renal, and musculoskeletal disorders, some of which independently contribute to an increased overall risk of death in these patients [5-7]. Despite the use of current therapies, many patients with COPD continue to experience exacerbations and a substantial symptom burden that impacts daily living and quality of life [8]. This underlines the need for new COPD treatment approaches.

In this narrative review, we describe the general pathophysiology, inflammatory processes, and current treatment paradigms for COPD and introduce dual inhibition of phosphodiesterase (PDE) 3 and PDE4 as a novel, broadly applicable treatment strategy for patients with COPD.

Pathophysiology and Inflammatory Processes in COPD

The manifestations of COPD are chronic in nature, and include pulmonary inflammation, airway remodeling, excessive mucus production, and destruction of lung parenchyma [1,9]. For most patients, COPD inflammatory disease involves the interplay of systemic and lung-specific inflammatory processes that contribute to its pathogenesis [10-12]. The inflammation in COPD is driven by exposure to cigarette smoke and other inhaled toxic pollutants and results in the

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production of cytokines and chemokines that activate both structural and inflammatory cells [10,11,13] involved in both the innate and adaptive immune responses, including tumor necrosis factor (TNF), interleukin 1β (IL-1β), granulocyte-macrophage colony-stimulating factor (GM-CSF), chemokine (C-X-C motif) ligand 8 (IL-8), and transforming growth factor β (TGF-β) [10-12]. Macrophages are also activated to release inflammatory mediators by cigarette smoke, and their density is markedly increased in the airways and lung parenchyma of patients with COPD [10-12]. Cigarette smoke has a direct stimulatory effect on granulocyte production and release from the bone marrow [12]. Accordingly, increased numbers of activated neutrophils can be found in the sputum and bronchoalveolar lavage fluid of patients with COPD. In addition, lymphocytes, including CD8+ T cells, CD4+ T cells, and B cells, have been identified in the lungs of patients with COPD, suggesting a potential role of altered immunity in the pathogenesis of this disease [10-12,14].

Cigarette smoke or bacterial or viral antigens activate these adaptive immune cells to release proteolytic enzymes and cytokines causing neutrophilic inflammation and inducing structural cell death [10-12]. Together, these pathologic responses cause the physiologic abnormalities commonly seen in patients with COPD, including ciliary dysfunction and airflow obstruction, which ultimately results in gas exchange abnormalities, functional disability, and, in extreme cases, pulmonary hypertension and respiratory insufficiency [9].

Current Therapies for COPD

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), the goals of the management and treatment of COPD are symptom reduction, improvement in lung function

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and quality of life, and mitigation of future risk of disease progression and exacerbations [1]. Based on current evidence, GOLD recommends a tailored treatment approach for COPD based on symptom burden and exacerbation risk [1]. Nonpharmacologic management includes identification and reduction of risk factor exposure (e.g., cigarette smoking and mitigation of environmental exposures), healthy lifestyle habits, and appropriate vaccinations. As COPD progresses, the patient may benefit from pulmonary rehabilitation, in some cases oxygen therapy, and, in a small number of patients, ventilatory support [1,4].

Currently, the central core of pharmacologic maintenance therapies for COPD consists of long-acting inhaled bronchodilators, which include 2 major classes: long-acting β_2 agonists (LABA) and long-acting muscarinic antagonists (LAMA). In some patients, the addition of inhaled corticosteroids (ICS) decreases the risk of exacerbations and their sequelae [15-17]. Bronchodilators, as single therapy or part of a dual regimen, are recommended as maintenance therapy across all patient groups [1]. For patients who are at increased risk of exacerbations (≥2/year or ≥1/year leading to hospitalization) and who have elevated blood eosinophil levels (≥100 cells or ≥300 cells/μL), GOLD recommends the addition of ICS in combination with dual long-acting bronchodilator therapy [1]. While dual bronchodilator therapy and to a greater extent triple therapy (dual bronchodilator + ICS) have been shown to improve lung function, relieve symptoms, and reduce exacerbations and possibly mortality risk in patients with COPD, around half of patients using triple therapy continue to experience both exacerbations and symptoms that impact their quality of life [1,8,18]. Real-world studies show that patients with COPD receiving either dual or triple maintenance therapy still have a substantial symptom burden and around 40% still experience ≥1 moderate or severe exacerbation per year [19-22]. In particular, patients are bothered by dyspnea, which was noted as the most impactful symptom on patients' daily

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activities and quality of life [21-23]. In addition, ICS therapy can be associated with adverse effects, including increased risk of pneumonia and, with long-term therapy, osteopenia, osteoporosis, hyperglycemia, and cataracts [24,25].

Recent studies have explored the potential role of biologics in select populations of patients with COPD. Initial large trials of mepolizumab [26] and benralizumab [27] demonstrated that these treatments failed to have an impact on the incidence of exacerbations, which was the primary outcome of those studies. However, subgroup analyses of the collected data suggested a beneficial effect in patients with high eosinophil count (>300 cells/dL). Subsequent trials with dupilumab have shown positive results in reducing exacerbation frequency compared to placebo in patients with repeated or severe exacerbations and elevated eosinophil counts [28]. Based on these results, the FDA has approved dupilumab as a medication with potential use in those patients on maximal conventional therapy who remain very symptomatic and continue to experience moderate or severe exacerbations. In addition, some preliminary data with the use of itepekimab, a monoclonal antibody with anti–IL-33 activity, has demonstrated decreased exacerbation rates in former smokers with COPD independent of blood eosinophil count, suggesting a potential benefit in those patients [29]. Several studies are underway with different biologics targeting type 2 inflammatory pathways, the readout of which will provide information about their specific use in COPD patients with severe disease who continue to exacerbate despite optimal medical therapy.

Methods of Drug Delivery in COPD

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Delivery of medications through the inhalation route has become the preferred method of drug delivery for COPD therapy, as it achieves a high drug concentration locally within the lungs to maximize the therapeutic effect [30,31]. Current inhalation delivery systems include handheld inhalers such as pressurized metered-dose inhalers (pMDIs), dry powder inhalers (DPIs), and soft mist inhalers (SMIs); these devices have the widest acceptance and are used by most patients with COPD [31]. However, the use of such delivery systems has been hampered by the fact that many patients commit critical errors during use, especially given that many patients with COPD have dexterity and cognitive problems. Nebulizers are a preferred mode of administration for medications in such groups of patients with COPD with cognitive, neuromuscular, or ventilatory impairments [31]. Furthermore, nebulizers have other advantages in elderly patients because they do not require patient coordination between inhalation or a generally optimal inspiratory flow rate, making them ideal for such patient populations [31]. Indeed, in patient and caregiver surveys, up to 80% of both patients and caregivers reported that using a nebulizer was better than using an inhaler (pMDI/DPI) [32,33].

Oral medications have also been widely used for the treatment of COPD. Macrolide antibiotics, which potentially have immunomodulatory and anti-inflammatory properties, have shown varying efficacies across several clinical studies that enrolled patients who continued to have acute exacerbations despite treatment with standard of care therapy [34]. Among the most studied macrolide antibiotics is azithromycin, which has been shown to decrease exacerbations, particularly in former smokers [34,35]. An alternative oral medication that has been shown to reduce risk of exacerbations in patients with COPD on optimal inhaled therapy is roflumilast, a PDE4 inhibitor that is somewhat limited in its use and tolerance, owing to its frequent gastrointestinal adverse effects [36,37]. In some regions of the world, the use of oral antioxidants

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is favored, as several randomized clinical trials of patients with COPD have shown significant reduction of exacerbation risk with use of carbocysteine and N-acetylcysteine [38].

Phosphodiesterases in COPD

PDEs are a superfamily of enzymes that are grouped into 11 subfamilies with different structures, substrate specificity, and regulatory mechanisms [39-41]. PDE enzymes catalyze the hydrolysis of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) [41,42]. cAMP and cGMP themselves are regulators of intracellular signal transductions that play an important role in regulating cell proliferation and differentiation, as well as inflammation and the immune response [41]. Given that COPD is an inflammatory disease, both cAMP and cGMP play critical roles in its pathogenesis [43].

Role of PDE4 in COPD

PDE4 is highly expressed in leukocytes and other inflammatory cells as well as in airway smooth muscle and pulmonary nerves [44,45]. As a cAMP-specific inhibitor, PDE4 plays a critical role in the regulation of the inflammatory response [39,43,45]. In patients with COPD, increased levels of PDE4 have been observed in inflammatory cells from the lungs, particularly in patients who are current smokers [46,47]. Therefore, PDE4 is a rational target to modulate aberrant inflammatory processes in COPD [44,48,49]. In vitro experiments have shown that inhibition of PDE4 suppresses airway inflammation by decreasing the release of inflammatory mediators and by inhibiting inflammatory and immune cell infiltration, thereby controlling their accumulation in the lungs [50-52]. It has further been demonstrated that PDE4 inhibitors can suppress the release of inflammatory mediators neutrophil elastase and matrix metalloproteinase-9 from

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primed neutrophils and TGF-β and TNF-α from primed macrophages [51,53]. These preclinical studies have also demonstrated that inhibition of PDE4 stimulates cystic fibrosis transmembrane conductance regulator (CFTR), increases ciliary function in bronchial epithelial cells [54], and decreases mucus hypersecretion through the suppression of key mucin genes [55]. In a guinea pig model of cigarette smoke–induced lung injury, PDE4 inhibition mitigated infiltration of macrophages and neutrophils into alveolar areas and small airways in the lungs [56].

PDE4 inhibition in COPD

Roflumilast, an oral PDE4 inhibitor, was approved in the US in 2010 as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations, and in Europe in 2011 for the treatment of severe COPD associated with chronic bronchitis in adult patients with a history of frequent exacerbations [48,57,58]. GOLD recommends roflumilast as an add-on treatment for patients on LABA + LAMA + ICS who continue to experience exacerbations [1], with recommended dosing of 250 mg once daily for 4 weeks followed by a maintenance dose of 500 mg per day [58]. Clinical studies (**Table 1**) have demonstrated that roflumilast significantly improved pulmonary function tests, reduced inflammatory cell load, and reduced the risk of exacerbations in patients with COPD [59,60]. AEs with roflumilast treatment were mild to moderate, the most common being gastrointestinal disorders (diarrhea and nausea) and weight loss [61]. A pooled safety analysis of 14 clinical trials showed that AEs with intermediate- and long-term treatment were generally similar compared to placebo [61]. However, real-world studies showed a much higher incidence of AEs, mainly related to gastrointestinal system, leading to frequent treatment discontinuation [62-64].

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Inhaled drug delivery methods represent a potential approach to reduce the gastrointestinal side effects associated with oral PDE4 inhibitors. A number of inhaled PDE4 inhibitors for the treatment of COPD have been evaluated in clinical trials, but their development was ultimately discontinued owing to limited efficacy [30]. These compounds include AWD-12-281, tofimilast, UK-500.001, and GSK256066, which showed promising preclinical results but demonstrated poor efficacy in clinical studies in patients with COPD [30]. Other inhaled PDE4 inhibitors, including SCH900182P, 12b, GS-5759, naphthyridinone, and pyridazinone, did not advance past preclinical development [30]. Currently, the only inhaled PDE4 inhibitor under clinical investigation for the treatment of COPD is tanimilast, a DPI administered twice daily [65]. Tanimilast is 10 times more potent in inhibiting PDE4 enzymatic activity compared with roflumilast [65], and it has been shown to significantly reduce inflammatory mediators in sputum compared with placebo yet with little effect on inflammatory cell numbers in the sputum or on blood inflammatory markers [66]. Results from the 24-week, dose-ranging, phase 2b PIONEER study of tanimilast as add-on maintenance therapy to the LABA formoterol showed that tanimilast had similar effects as placebo on lung function (forced expiratory volume in 1 s [FEV_1]), symptom-related endpoints, and rescue medication usage; however, post hoc analyses demonstrated a numerically larger exacerbation rate reduction in patients with a chronic bronchitis phenotype compared to the overall population (24%–37% reduction) [67]. Tanimilast was well tolerated in all treatment groups, and the rate of gastrointestinal AEs was low and comparable to placebo [67]. Two phase 3 studies evaluating the efficacy and safety of tanimilast as an add on to triple maintenance therapy (LAMA + LABA + ICS) in patients with COPD and chronic bronchitis are currently ongoing (**Table 1**) and slated to have final readouts in the near future.

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Role of PDE3 in COPD

PDE3 is expressed in the lung epithelium, endothelium, smooth muscle cells, and inflammatory cells [45,68]. It is the major PDE present in vascular smooth muscle cells and plays a significant role in maintaining smooth muscle tone [45,69,70]. Accordingly, preclinical studies have shown that inhibition of PDE3 relaxes smooth muscle cells and inhibits allergic airway inflammation [68,71]. In a guinea pig model of histamine- and acetylcholine-induced tracheal tension, PDE3 inhibition antagonized the contractional ability of histamine [71]. Moreover, in a house dust mite–driven asthma mouse model, the PDE3 inhibitor enoximone had significant reductions in lung inflammatory cell numbers including eosinophils, macrophages, and T cells compared with mice treated with phosphate-buffered saline [68]. Clinical studies in patients with asthma demonstrate the efficacy of the PDE3 inhibitor olprinone in inducing bronchodilation as measured by mean increases in FEV_1 [72,73]. However, despite these promising preclinical and limited clinical data in asthma, there is currently no single-action PDE3 inhibitor in development for COPD. Therefore, there remains limited clinical evidence of the efficacy of this drug class in COPD.

Dual PDE3/4 Inhibition in COPD

Together, inhibition of both PDE3 and PDE4 may have additive or synergistic anti-inflammatory and bronchodilator effects, as both are expressed in inflammatory cells and lung structural cells [39]. Indeed, dual inhibition of PDE3 and PDE4 has shown enhanced or synergistic effects on

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the anti-inflammatory response and airway smooth muscle relaxation compared with either PDE3 or PDE4 alone (**Figure 1**) [74-76].

Ensifentrine is a novel, selective, dual-action, inhaled inhibitor of PDE3 and PDE4 that was approved by the US Food and Drug Administration (FDA) in June 2024 for the maintenance treatment of COPD in adult patients. Preclinical studies have demonstrated the anti-inflammatory activity and bronchodilator effects of ensifentrine [77,78]. Guinea pig models of allergic bronchoconstriction have demonstrated that inhaled ensifentrine significantly reduced inflammatory cell recruitment into the bronchoalveolar lavage fluid and nasal passages [77,78]. Furthermore, pretreatment with inhaled ensifentrine inhibited antigen-induced eosinophil migration by >80% [77]. A phase 2b randomized, double-blind, placebo-controlled, dose-ranging study in patients with COPD demonstrated that, compared with placebo, treatment with nebulized ensifentrine monotherapy significantly increased bronchodilation as evidenced by increased FEV_1 at 1 day and at 4 weeks after dosing and progressively improved patient symptoms and health-related quality of life as measured by Evaluating Respiratory Symptoms in COPD (E-RS) and St. George's Respiratory Questionnaire–COPD Specific (SGRQ-C) total scores, respectively [79]. Importantly, there were also substantial improvements in dyspnea after 4 weeks, as measured by the Transition Dyspnea Index (TDI) [66,79]. Overall, the frequency of AEs with ensifentrine was similar to placebo, and treatment-related AEs were limited, with no gastrointestinal or cardiovascular treatment-related AEs observed [79]. Randomized, double-blind, placebo-controlled phase 2 studies have evaluated ensifentrine in conjunction with other bronchodilators in patients with COPD [80,81]. A significantly greater increase in FEV_1 was observed in patients treated with ensifentrine in conjunction with salbutamol (mean 295 mL;

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p<0.0001) or ipratropium (mean 292 mL; p<0.0001) compared to treatment with either bronchodilator alone (mean 108 mL and mean 94mL with salbutamol or ipratropium alone, respectively) [81]. In a 3-day study, ensifentrine also produced a significant improvement in peak FEV_1 when combined with the LAMA tiotropium (mean 477 [p=0.002] and 500 mL [p<0.0001]) with ensifentrine 1.5 and 6 mg, respectively) compared with tiotropium alone (mean 373 mL); similar results were recapitulated in a 4-week, dose-ranging study of ensifentrine on top of tiotropium maintenance therapy [80,81]. Patients treated with the combination of ensifentrine and tiotropium also had statistically significant improvements in SGRQ-C scores at 4 weeks compared with patients treated with tiotropium alone [80]. In all studies, ensifentrine was well tolerated and the addition of ensifentrine to bronchodilators did not change the AE profile [79-81].

These promising results in early-phase clinical studies led to 2 large, randomized, double-blind, placebo-controlled, phase 3 studies: ENHANCE (Ensifentrine as a Novel Inhaled Nebulized COPD Therapy)-1 and ENHANCE-2 [82]. In these studies, the efficacy and safety of ensifentrine (3 mg) vs placebo was measured on twice-daily administration for 24 weeks via a standard jet nebulizer in patients with symptomatic, moderate to severe COPD (**Table 1**) [82]. The ENHANCE program enrolled a broad population of patients, mostly those with moderate to severe COPD who were receiving maintenance therapy. Patients aged 40 to 80 years were randomized and treated in ENHANCE-1 (N=763) and ENHANCE-2 (N=790) across 17 countries and from 250 research centers and pulmonary practices [82]. More than half of patients in both trials were also receiving LABA or LAMA with or without ICS (69% and 55% in ENHANCE-1 and ENHANCE-2 respectively) [82]. The primary endpoint was met in both

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ENHANCE-1 and ENHANCE-2, as treatment with ensifentrine significantly improved FEV_1 area under the concentration time curve from 0 to 12 hours (AUC_{0-12h}) at week 12, with placebo-corrected increases from baseline of 87 mL in ENHANCE-1 ($p<0.001$) and 94 mL in ENHANCE-2 ($p<0.001$) [82]. Mean E-RS and SGRQ total scores were also improved vs placebo in patients treated with ensifentrine and exceeded the minimally clinically important differences in both trials, and ensifentrine treatment also resulted in significant improvements in dyspnea as measured by TDI scores [82]. Both studies showed reductions in daily rescue medication usages and COPD exacerbations with ensifentrine [82]. The rate of moderate or severe exacerbations over 24 weeks was reduced by 36% in ENHANCE-1 (nominal $p=0.05$) and by 43% in ENHANCE-2 (nominal $p<0.01$) with ensifentrine treatment compared with placebo [82]. Efficacy results were similar to the overall population in patients receiving concomitant LAMA or LABA, with or without ICS. These efficacy results were further demonstrated over 48 weeks in a subset of patients in ENHANCE-1 [82]. In both trials, ensifentrine was well tolerated and a similar proportion of treatment-emergent AEs were reported in patients receiving ensifentrine (38.4% in ENHANCE-1 and 35.3% in ENHANCE-2) and placebo (36.4% in ENHANCE-1 and 35.4% in ENHANCE-2) [82]. Gastrointestinal adverse events (AEs) were similar in both treatment groups and no differences were observed in safety laboratory tests, electrocardiogram parameters, or vital signs [82]. Given the significant improvements in lung function in patients with moderate to severe COPD and the favorable AE profile, ensifentrine has been approved by the FDA as a maintenance treatment in this patient population [83]. The approval of ensifentrine for the treatment of patients with symptomatic moderate to severe COPD is important as it represents the first inhaled product with a novel mechanism of action that has been approved for the treatment of COPD in >20 years [83]. Its introduction into the armamentarium for COPD has

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given patients and healthcare practitioners an alternative treatment option, taken alone or in combination with other inhaled maintenance therapies, that effectively reduces exacerbation rate and risk [84] and achieves clinically meaningful improvements in dyspnea [85] in a broad population of patients with COPD.

Conclusions

Despite numerous currently available maintenance therapies for COPD, the continued presence of symptoms and risk for exacerbation in patients with COPD underscores the need for new treatment approaches. In the lungs, PDE3 and PDE4 play important roles in inflammation and airway smooth muscle contraction that is evident in conditions such as COPD. Dual inhibition of PDE3 and PDE4, particularly with a nebulized mode of delivery, may provide clinical benefit to a broad range of patients with COPD and represents a promising new treatment strategy. Future clinical trials assessing the efficacy of dual PDE3 and PDE4 inhibition in combination with ICS and its positioning in the pharmacological armamentarium to treat patients with COPD are warranted.

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Author contributions

All authors contributed to concept and design, analysis and interpretation, and drafting and revising the manuscript for important intellectual content. All authors approved the final version of the manuscript for publication.

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Declarations of Interest

BC has received fees from GlaxoSmithKline and AstraZeneca for consulting, speaking at meetings, and participating in advisory boards; from Menarini for consulting and speaking at meetings; from Sanofi Aventis and Verona for consulting and participating in advisory boards; from Axios for consulting; and from Chiesi and Regeneron for lectures, presentations, speakers bureaus, manuscript writing, or educational events; has received support for attending meetings and/or travel from GlaxoSmithKline and Sanofi Aventis; and has participated in a Data Safety Monitoring Board or Advisory Board for AZ Therapeutics, Sanofi Aventis, and Vertex. **NAH** has received honoraria for serving as a consultant or board

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Table 1. Late-Phase Clinical Trial Designs of PDE4 and PDE3/4 Inhibitors in COPD

Compound	Inhibitor type and mode of delivery	Study	NCT number	Trial design	Patients	Primary endpoint
Roflumilast	**PDE4** **oral tablets**	RELIANCE Roflumilast or azithromycin to prevent COPD exacerbations	04069312	• Phase 3 • Randomized, parallel-group, non-inferiority • 250 µg/day × 4 weeks, then 500 µg/day (or alternate regimen)for 6–72 months	• N=1200 • Age ≥40 y • Severe COPD with chronic bronchitis • On LABA, LABA/LAMA, or ICS/LABA maintenance therapy	• All-cause hospitalization • All-cause deaths
Tanimilast	**PDE4** **Inhaled with dry powder inhaler**	ARGO Effectiveness of roflumilast treatment in Greek patients with COPD	05426915	• Prospective, observational	• N=750 • Severe COPD with chronic bronchitis • History exacerbations on maintenance therapy	• Changes in Clinical COPD Questionnaire at 3, 6, 9, and 12 months
		PILASTER Tanimilast add-on to triple therapy in patients with COPD and chronic bronchitis	04636801	• Phase 3 • Randomized, double-blind, placebo-controlled • 1600 µg or 3200 µg total/day	• N=3435 • COPD with chronic bronchitis • History of exacerbations on maintenance therapy	• Moderate and severe exacerbations
		PILLAR Tanimilast add-on to triple therapy in patients with COPD and chronic bronchitis	04636814	• Phase 3 • Randomized, double-blind, placebo- and active-controlled (roflumilast) • 1600 µg or 3200 µg total/day	• N=3980 • COPD with chronic bronchitis • History of exacerbations on maintenance therapy	• Moderate and severe exacerbations
Ensifentrine	**Dual PDE3/PDE4** **Inhaled with standard jet nebulizer**	ENHANCE-1 Ensifentrine in patients with moderate to severe COPD	04535986	• Phase 3 • Randomized, double-blind, placebo-controlled • 3 mg BID	• N=763 • Age ≥40–80 y • Moderate to severe COPD • On no or stable maintenance therapy	• Least squares mean change from baseline in FEV_1 AUC_{0-12h} at week 12
		ENHANCE-2 Ensifentrine in patients with moderate to severe COPD	04542057	• Phase 3 • Randomized, double-blind, placebo-controlled • 3 mg BID	• N=790 • Age ≥40–80 y • Moderate to severe COPD • On no or stable maintenance therapy	• Least squares mean change from baseline in FEV_1 AUC_{0-12h} at week 12

AUC_{0-12h}, area under the concentration time curve from 0 to 12 hours; BID, twice daily; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; ICS,

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inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; PDE, phosphodiesterase.

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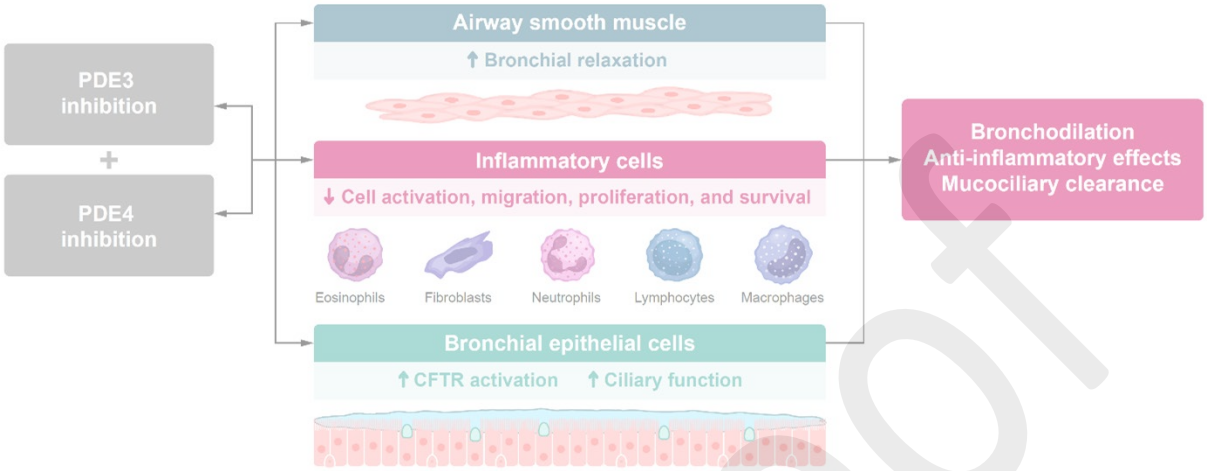
Figure 1. Mechanisms of Action of PDE3/4 Inhibitors. CFTR, cystic fibrosis transmembrane conductance regulator; PDE, phosphodiesterase.



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