

New Therapies for Treatment of Chronic Obstructive Pulmonary Disease

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Approximately 10% of individuals who are 40 years of age or older have Chronic Obstructive Pulmonary Disease (COPD).¹ In the United States, COPD is consistently ranked among the top causes of death, with mortality rates of more than 120,000 individuals each year.² As a result, COPD has high healthcare utilization with frequent clinician office visits, multiple hospitalizations due to acute exacerbations, and the need for chronic therapy.³

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) annually updates guidance for the management of COPD. The 2023 guideline included revised strategies for pharmacologic COPD treatment based upon new Gold Group Classifications.⁵ In addition, recommendations for the use of triple inhaler therapy in the updated GOLD "ABE" groups was introduced with the 2023 guidance.⁵ Since the publication of that guideline, 2 new therapies have received Food and Drug Administration (FDA) approval for maintenance treatment of COPD. This newsletter will review the evidence for these therapies and discuss their role in COPD management. The 2025 GOLD guidance will also be briefly reviewed to describe the place in therapy for the 2 new COPD treatments.

Assessment of COPD Treatments

Outcomes to assess the effectiveness of COPD therapies include changes in lung function, quality of life, dyspnea, COPD exacerbation rate and/or severity, and frequency of adverse events. The most common surrogate outcome used in studies to determine treatment effectiveness is post-bronchodilator forced expiratory volume in one second (FEV₁).⁵ The minimal clinically important difference (MCID) in FEV₁ values for COPD changes have not been clearly defined, but research in COPD patients suggest that the minimally important FEV₁ change is 120 mL.⁵ The St. George Respiratory Questionnaire (SGRQ) is used to determine the effects of COPD on quality of life (QoL) with scores ranging from 0 to 100.⁶ Higher scores on the SGRQ indicate more QoL limitations.⁶ The MCID on the SGRQ is an improvement of 4 points.⁶

Treatment of COPD

Goals of COPD therapy include symptom relief, improved exercise tolerance, slowed disease progression, and reduced exacerbations. The GOLD report uses the core metrics of dyspnea severity and frequency of exacerbations to categorize patients into GOLD "ABE" groups for initial pharmacologic management.⁵ For patients in Group A (mild COPD), therapy should be initiated with a short-acting or long-acting bronchodilator.⁵ Patients with more severe COPD in Group B

should be started on combined long-acting beta-agonist (LABA) and long-acting muscarinic antagonist (LAMA) inhaler therapy.⁵ For patients in Group E (severe COPD with frequent exacerbations), an inhaled corticosteroid (ICS) may be added to LABA/LAMA therapy if blood eosinophils are greater than 300 cells/ μ L.⁵ Long-term monotherapy with a ICS is not recommended, and triple LABA/LAMA/ICS inhaler therapy is preferred over LABA/ICS therapy to minimize adverse events associated with steroid therapy.⁵

Roflumilast, an oral phosphodiesterase (PDE)-4 inhibitor, is FDA-approved to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations.⁷ Data show that roflumilast may have greater benefit in patients with a prior history of hospitalization for an acute COPD exacerbation.⁵ The 2023 GOLD guidance provides an algorithm for follow-up pharmacologic treatment where management is based on 2 key treatable traits: persistence of dyspnea and occurrence of exacerbations.⁵ Roflumilast is included in this algorithm for COPD patients who are adequately treated with LABA/LAMA/ICS therapy, but continue to have yearly exacerbations, FEV₁ less than or equal to 50%, and chronic bronchitis.⁵

The GOLD guidance recommends the use of roflumilast as add-on maintenance therapy to prevent exacerbations; it is not recommended for improvement in other COPD outcomes.⁵ In the Fee-for-Service (FFS) Oregon Health Plan (OHP), providers must submit a prior authorization (PA) request to ensure oral roflumilast is prescribed for patients with severe or very severe COPD, chronic bronchitis and yearly exacerbations despite treatment with an ICS and long-acting inhaler treatment (LABA or LAMA).

New COPD Therapy: OHTUVAYRE (Ensifentrine)

In June 2024, ensifentrine, a dual PDE-3 and PDE-4 inhibitor, received FDA-approval for maintenance treatment of COPD in adults at a dose of 3 mg by inhaled jet nebulizer twice daily.⁸ Due to dual inhibition of PDE, ensifentrine has anti-inflammatory activity and bronchodilator effects.⁸ It is not indicated for use as rescue therapy for immediate relief during a COPD exacerbation.⁸ The efficacy of ensifentrine was evaluated in two phase 3 trials (ENHANCE-1 and ENHANCE-2).⁹ Patients enrolled in the 2 randomized controlled trials (RCTs) were 40 to 80 years of age, with moderate to severe COPD, with a post-bronchodilator FEV₁ 30% to 70%, and a smoking history of 10 or more pack-

years.⁹ In ENHANCE-1, patients were a mean age of 65 years, with a mean postbronchodilator predicted FEV₁ of 52%, 57% were current smokers, and 25% of patients reported COPD exacerbations within 15 months prior to the study.⁹ Patients in ENHANCE-2 were a mean age of 65 years, with a mean postbronchodilator predicted FEV₁ of 51%, 55% were current smokers, and 21% of patients reported COPD exacerbations within the 15 months prior to the study.⁹ In both trials, patients could receive concurrent LAMA or LABA therapy with or without an ICS but were ineligible if receiving a LAMA/LABA or a LAMA/LABA/ICS.⁹

The primary endpoint in these trials was impact on bronchodilation from baseline to week 12 as assessed by the change FEV₁ area under the curve from 0 to 12 hours (AUC_{0-12h}).⁹ Compared with placebo, ensifentrine improved the least squares mean (LSM) change in FEV₁ AUC_{0-12h} from baseline to week 12 in both RCTs (moderate quality evidence).⁹ Study results are presented in **Table 1**.

Table 1. ENHANCE Trials: LSM Change in FEV₁ AUC_{0-12h}^{9,10}

Trial	Placebo (mL)	Ensisfentrine (mL)	Difference (mL)
ENHANCE-1	-26	61	87 (95% CI 55 to 119) p<0.0001
ENHANCE-2	-46	48	94 (95% CI 65 to 124) p<0.0001

Abbreviations: CI = confidence interval; FEV₁ AUC_{0-12h} = forced expiratory volume area under the curve; LSM = least square mean change

Adverse reactions that occurred in people treated with ensifentrine included back pain, hypertension, urinary tract infection, and diarrhea.⁹ Treatment with ensifentrine is also associated with an increased risk of psychiatric adverse reactions.⁸ Before initiating treatment with ensifentrine, healthcare providers should carefully weigh the risk and benefits of treatment in patients with a history of depression and/or suicidal thoughts or behavior, and re-evaluate the risks and benefits of continuing treatment if such events occur.⁸ The oral PDE-4 inhibitor, roflumilast also carries this warning in the prescribing information.⁷

Ensisfentrine was not studied with some inhaler regimens that are currently recommended for treatment of COPD. Patients receiving concurrent LAMA/LABA inhaler, which is recommend as first-line therapy for patients with moderate COPD, and patients with triple therapy (LAMA/LABA/ICS) were excluded from enrollment. This may limit generalizability of the results from these trials.¹¹ Head-to-head clinical trials with ensifentrine and other COPD maintenance medications have not been conducted. Additional data is needed to assess the impact of ensifentrine on COPD exacerbations, hospitalizations, and quality of life. Ensisfentrine is included in the 2025 GOLD update as add-on maintenance medication in COPD patients who continue to have dyspnea despite use of LABA/LAMA therapy.¹²

The authors noted that ensifentrine significantly improves lung function, (high-quality evidence), dyspnea (high-quality evidence) and health status (moderate-quality evidence).¹²

Dupilumab Expanded Indication in COPD

In September 2024, DUPIXENT (dupilumab), a targeted immune modulator (TIM), received an expanded FDA-approved indication as an add-on maintenance treatment for adults with inadequately controlled COPD.¹³ Dupilumab is already approved for use in patients with moderate-to-severe asthma characterized by an eosinophilic phenotype or with oral corticosteroid dependent asthma.¹³ The FDA based the approval on pooled data from 2 RCTs (BOREAS and NOTUS) conducted in adults with COPD and chronic bronchitis who were receiving triple inhaler therapy (LAMA/LABA/ICS).^{14,15} Trial enrollment required an exacerbation history of at least 2 moderate or 1 severe exacerbation(s) in the previous year despite receiving maintenance triple inhaler therapy (ICS/LABA/LAMA) and symptoms of chronic productive cough for at least 3 months in the past year.^{14,15}

In the BOREAS trial, 939 patients with COPD who had a blood eosinophil count ≥ 300 cells/μL and an elevated exacerbation risk were randomized to dupilumab 300 mg or placebo subcutaneously (SC) every 2 weeks.¹⁴ The mean number of moderate or severe COPD exacerbations for the enrolled population in the previous year was 2.3.¹⁴ The primary end point was the annualized rate of moderate or severe COPD exacerbations at 52 weeks.¹⁴ The annualized rate of moderate or severe exacerbations was 0.78 with dupilumab and 1.10 with placebo (rate ratio [RR], 0.70; 95% CI, 0.58 to 0.86; p<0.001).¹⁴ The prebronchodilator FEV₁ increased from baseline to week 12 by a LSM of 160 mL with dupilumab and 77 mL with placebo (LSM difference, 83 ml; 95% CI, 42 to 125; P<0.001).¹⁴ The MCID for this change is 120 mL.⁵ At week 52, the SGRQ score had improved by a LSM of -9.7 with dupilumab and -6.4 with placebo (LSM difference, -3.4; 95% CI, -5.5 to -1.3; P=0.002). This change was statistically significant, but did not meet the MCID of 4 points.

In the NOTUS trial, which enrolled a similar population, the mean number of moderate or severe COPD exacerbations in the previous year was 2.1.¹⁵ The annualized rate of moderate or severe exacerbations after 52 weeks was 0.86 with dupilumab and 1.30 with placebo (RR, 0.66; 95% CI, 0.54 to 0.82; p<0.001).¹⁵ The prebronchodilator FEV₁ increased from baseline to week 12 with dupilumab (LSM change, 139 ml) as compared with placebo (LSM change 57 ml), with a LSM difference at week 12 of 82 ml (95% CI 40 to 124; P<0.001) and at week 52 of 62 ml (95% CI 11 to 113; P=0.02).¹⁵ At week 52, the decrease from baseline in SGRQ

total score (indicating quality of life improvement) was -9.8 points in the dupilumab group and -6.4 points in the placebo group (LSM difference, -3.4 points; 95% CI, -5.8 to -0.9).¹⁵ This change was statistically significant but did not meet the MCID of 4 points.¹⁵

In both trials, the incidence of adverse events (AEs) was similar in between dupilumab and placebo and consistent with the established profile of dupilumab.^{14,15} Dupilumab has been added to the 2025 GOLD guidelines, as an add-on treatment in patients maintained on LABA/LAMA/ICS therapy who are still experiencing exacerbations with symptoms of chronic bronchitis.¹² Mepolizumab (NUCALA), another TIM, recently received FDA-approval in May 2025 as an add-on maintenance treatment in adults with poorly controlled COPD and an eosinophilic phenotype.

Oregon Health Plan Policies

The evidence for ensifentrine and dupilumab in treating COPD was presented to the Oregon Pharmacy and Therapeutic Committee at their December 2024 meeting. The committee approved recommendations to implement PA criteria for both therapies to verify appropriate place in therapy for patients enrolled in the FFS OHP (see **Figure 1**).

Preferred ICS/LABA inhalers on the FFS Preferred Drug List (PDL) include budesonide/formoterol; fluticasone/salmeterol and mometasone/formoterol. Preferred LAMA/LABA inhalers include umeclidinium/vilanterol and tiotropium/olodaterol. Non-preferred LABA, LAMA/LABA, and LAMA/LABA/ICS inhalers require PA.

Figure 1. Oregon Health Plan Prior Authorization Criteria for Dupilumab and Ensifentrine

- Dupilumab: Restrict use to adults with inadequately controlled COPD on triple inhaler therapy (LABA/LAMA/ICS).
- Ensifentrine: Ensure patient is using guideline directed therapy prior to adding ensifentrine nebulizer to therapeutic regimen of LABA or LAMA inhaler or ICS.

Conclusion

COPD has high healthcare utilization with frequent clinician office visits, multiple hospitalizations due to acute exacerbations, and the need for chronic medication therapy. Adhering to guideline-directed therapeutic recommendations can reduce COPD symptoms, decrease the risk of frequent exacerbations and improve quality of life for people living with COPD.¹² Two new therapies, dupilumab and ensifentrine, were recently approved by the FDA to enhance maintenance

treatment of COPD. Comparative trials with other COPD maintenance medications have not been conducted with either agent. However, these medications provide additional treatment options for patients with frequent COPD exacerbations despite optimized inhaler therapy. Both medications are included as therapeutic options in the 2025 GOLD update.¹² Dupilumab is cited as an intervention that reduces the frequency of COPD exacerbations in patients maintained on triple inhaler therapy.¹² Ensifentrine is included as an option for add-on maintenance therapy in patients with COPD who continue to have dyspnea despite LABA/LAMA therapy.¹²

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