JAMA Clinical Guidelines Synopsis

Inhaled Pharmacotherapy for Stable COPD

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GUIDELINE TITLE 2025 Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2025 GOLD report)

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DEVELOPER AND FUNDING SOURCE Global Initiative for Chronic Obstructive Lung Disease (GOLD)

TARGET POPULATION Adults with chronic obstructive pulmonary disease (COPD)

MAJOR RECOMMENDATIONS

- For patients with mild symptoms and infrequent exacerbations (GOLD group A), monotherapy with a long-acting bronchodilator is suggested over short-acting bronchodilators as initial therapy (level of evidence [LOE] A).
- For patients with more symptoms (GOLD group B) or frequent exacerbations (GOLD group E), a long-acting β_2 agonist (LABA) with a long-acting muscarinic antagonist (LAMA) are recommended as initial therapy (LOE A).
- The initial assessment of patients diagnosed with COPD should include a blood absolute eosinophil count (AEC) (ungraded recommendation).
- For patients experiencing 1 or more exacerbations per year despite proper use of a combined LABA-LAMA regimen, addition of an inhaled corticosteroid (ICS) is recommended as escalation therapy if blood AEC is 100/μL or higher (LOE A).

Summary of the Clinical Problem

COPD is a lung condition characterized by respiratory symptoms due to abnormalities of the airways or alveoli that cause persistent airflow obstruction. Globally, COPD is estimated to affect 10.3% of adults aged 25 years or older.[1] COPD exacerbations are defined as episodes of increased dyspnea and/or cough. Moderate exacerbations are those requiring short-acting bronchodilators and oral corticosteroids but not an emergency department (ED) visit or hospitalization. Severe exacerbations involve an ED visit or hospitalization. Stable COPD is defined as COPD not in an active exacerbation. The goals of treatment are symptom and exacerbation risk reduction.

Multimedia

Supplemental content

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To classify patients with stable COPD and guide pharmacotherapy, the 2025 GOLD report recommends using the ABE assessment tool, which replaced the ABCD scale in the 2023 GOLD report. Patients with 2 or more moderate exacerbations or 1 hospitalized exacerbation per year are placed into the highest risk group for exacerbations (group E; previously groups C and D). Patients with less than 2 moderate exacerbations per year are grouped by severity of symptoms using the COPD Assessment Test (CAT) or modified Medical Research Council (mMRC) dyspnea scales (group A, CAT <10 or mMRC 0-1; group B, CAT ≥10 or mMRC ≥2).

Characteristics of the Guideline Source

GOLD is a collaboration of clinical and research leaders convened by the National Institutes of Health and World Health Organization that reviews published research on COPD management and provides an annual GOLD report update.[2] Conflicts of interest are published on the GOLD website, and quality-of-evidence methodology is detailed in the report (eTable in the Supplement).

Evidence Base

Choice of initial inhaled pharmacotherapy in stable COPD is based on symptoms and exacerbation frequency. All patients with COPD should be offered a short-acting bronchodilator for immediate symptomatic relief. For GOLD group A, monotherapy with a long-acting bronchodilator (LAMA or LABA) is preferred over short-acting agents. In the INVIGORATE trial, which included 3444 patients with 1 or more moderate or severe exacerbations in the past year, those randomized to tiotropium (LAMA) had fewer exacerbations per year compared with those randomized to indacaterol (LABA) (0.73 vs 0.90; rate ratio, 0.81; 95% CI, 0.73-0.89).[3] Similarly, the POET-COPD trial (n = 7376) reported that patients randomized to the LAMA tiotropium had fewer exacerbations per year compared with the LABA salmeterol (0.64 vs 0.72; rate ratio, 0.89; 95% CI, 0.83-0.96).[4] Some trials suggest LAMA over LABA monotherapy, but the report notes that both improve lung function with similar safety profiles.

The combination of a LABA and LAMA is recommended as initial therapy for patients with COPD in GOLD groups B and E. In a randomized trial of 2431 patients meeting GOLD group B criteria, combined LABA-LAMA therapy was associated with improved lung function, and 55% had sustained improvement in symptom scores (≥2-unit CAT reduction at 24 weeks) vs a LABA alone (50% sustained improvement; odds ratio, 1.23; 95% CI, 1.01-1.50) or a LAMA alone (48% sustained improvement; odds ratio, 1.35; 95% CI, 1.11-1.65).[5] In a network meta-analysis of 99 studies among patients meeting group E criteria (n = 101 311), LABA-LAMA therapy was associated with fewer COPD exacerbations vs a LABA alone (hazard ratio [HR], 0.70; 95% credible interval [CrI], 0.61-0.80), a LAMA alone (HR, 0.87; 95% CrI, 0.78-0.99), or an ICS with a LABA (HR, 0.86; 95% CrI, 0.76-0.99).[6]

With more than 30 versions of inhaled therapies, choice of specific inhaled therapy should be individualized, considering cost and patient dexterity, inspiratory strength, and cognition.[2] After initiating inhaler therapy, GOLD recommends assessment of clinical response, adherence, and inhaler technique. Inhaler instruction should be provided at follow-up and before declaring therapy failure.[2]

If there is an inadequate response to inhaled therapy, the 2025 GOLD report recommends targeting the predominant treatable

condition: dyspnea or COPD exacerbations. For patients who are using LAMA or LABA monotherapy correctly but have poorly controlled dyspnea, escalation to LABA-LAMA combination therapy is recommended.[5] For patients with dyspnea despite use of LABA-LAMA therapy, nonpharmacological options, such as pulmonary rehabilitation, should be considered.

Escalation of inhaler therapy for continued exacerbations, defined as 1 or more exacerbations per year, should be guided by blood AEC. A post hoc analysis of 3 trials (4528 patients with ≥1 exacerbation in the prior year) found that adding an ICS (budesonide, 160 µg) to a LABA reduced exacerbations to 0.74 (95% CI, 0.62-0.87) per year from 1.05 (95% CI, 0.82-1.34) per year with a LABA alone.[7] Among patients taking LABA-ICSs, those with a higher baseline AEC had greater reduction in exacerbations compared with a LABA alone (25% mean reduction for AECs 100-190/µL; 26%-50% reduction for AECs 200-340/µL; 51%-60% reduction for AECs 350-630/µL).[7] No significant difference in exacerbation rates were reported with addition of an ICS to a LABA vs a LABA alone in patients with an AEC less than 100/µL (exacerbation rate ratios, 0.78-1.25).[7] Patients who have continued exacerbations with LAMA or LABA monotherapy and have AECs less than 300/µL should be prescribed LABA-LAMA therapy, and those with AECs of 300/µL or higher should be prescribed LABA-LAMA-ICS therapy. For patients with AECs of 100/µL or higher and continued exacerbations while taking LABA-LAMA therapy, addition of an ICS should also be considered. This escalation is supported by the ETHOS trial (8509 patients with moderate to very severe COPD and ≥1 exacerbation in the past year [57% group E]), which compared triple-inhaler therapy (LABA-LAMA-ICS) with dual bronchodilator therapy (LABA-LAMA).[8] The all-cause mortality rate was 46% lower with LABA-LAMA-ICS vs LABA-LAMA (28 vs 49 deaths; HR, 0.54; 95% CI, 0.34-0.87).[8]

The 2025 GOLD report provides guidance for transitioning from LABA-ICS to recommended therapy. LABA-ICS should be converted to LABA-LAMA for patients with AECs less than 100/µL or no history of exacerbations. Additionally, an ICS should be considered for deescalation in patients with pneumonia or adverse effects such as recurrent oral candidiasis or dysphonia. Caution is advised with ICS withdrawal in patients with AECs of 300/µL or higher as these patients had greater exacerbation risk than those continuing an ICS (rate ratio, 1.86; 95% CI, 1.06-3.29).[9] Continuation of LABA-ICS may be considered for those with controlled dyspnea and fewer exacerbations with an ICS (ie, positive treatment response).

Benefits and Harms

Symptoms and exacerbation rates for patients with COPD are decreased with guideline-recommended use of inhaled pharmacotherapy. The 2025 GOLD report notes that LABAs may cause resting sinus tachycardia and increase cardiac arrythmias, as well as tremors in older patients. The most common anticholinergic adverse effect of LAMAs is dry mouth. Use of ICSs is associated with increased risk of pneumonia. In a network meta-analysis of 7 trials with a duration of 6 months or longer (6235 patients with COPD), pneumonia was diagnosed in 234 patients taking placebo vs 345 patients treated with an ICS (odds ratio, 1.56; 95% CI, 1.3-1.86). Notably, the finding of increased pneumonia was largely driven by higher doses of ICS (≥1000 µg/d of beclomethasone).[10]

Discussion

Compared with earlier GOLD reports, the new guidelines place greater emphasis on the importance of using eosinophils as a biomarker to guide initiation, escalation, and withdrawal of ICS. Although this synopsis focuses on recommendations for inhaled therapies for stable COPD, the GOLD report continues to highlight the important role of nonpharmacological approaches, including smoking cessation, vaccination, and pulmonary rehabilitation.

Areas in Need of Future Study or Ongoing Research

Ensifentrine, a novel inhaled phosphodiesterase 3 and 4 inhibitor, enhances lung function and reduces dyspnea, but further studies are needed to evaluate its effect in combination with other inhaled therapies. Inhalers equipped with sensors and biofeedback training, termed *digital inhalers*, have been shown to improve inhaler technique and adherence in asthma, highlighting their potential for patients with COPD. While telemedicine improves accessibility and feasibility of COPD care, research is necessary to establish best practices for inhaler prescription and education by telemedicine.

ARTICLE INFORMATION

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