AMERICAN THORACIC SOCIETY DOCUMENTS

Pharmacologic Management of Chronic Obstructive Pulmonary Disease

An Official American Thoracic Society Clinical Practice Guideline: Executive Summary

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This official clinical practice guideline was approved by the American Thoracic Society February 2020

Background: This document provides clinical recommendations for the pharmacologic treatment of chronic obstructive pulmonary disease (COPD). It represents a collaborative effort on the part of a panel of expert COPD clinicians and researchers along with a team of methodologists under the guidance of the American Thoracic Society.

Methods: Comprehensive evidence syntheses were performed on all relevant studies that addressed the clinical questions and critical patient-centered outcomes agreed upon by the panel of experts. The evidence was appraised, rated, and graded, and recommendations were formulated using the Grading of Recommendations, Assessment, Development, and Evaluation approach.

Results: After weighing the quality of evidence and balancing the desirable and undesirable effects, the guideline panel made the following recommendations: *1*) a strong recommendation for the use of long-acting β_2-agonist (LABA)/long-acting muscarinic antagonist (LAMA) combination therapy over LABA or LAMA monotherapy in patients with COPD and dyspnea or exercise intolerance; *2*) a conditional recommendation for the use of triple therapy with inhaled corticosteroids (ICS)/LABA/LAMA over dual therapy with LABA/LAMA in patients with COPD and dyspnea or exercise intolerance who have experienced one or more exacerbations in the past year; *3*) a conditional recommendation for ICS withdrawal for patients with COPD receiving triple therapy (ICS/LABA/LAMA) if the patient has had no exacerbations in the past year; *4*) no recommendation for or against ICS as an additive therapy to long-acting bronchodilators in patients with COPD and blood eosinophilia, except for those patients with a history of one or more exacerbations in the past year requiring antibiotics or oral steroids or hospitalization, for whom ICS is conditionally recommended as an additive therapy; *5*) a conditional recommendation against the use of maintenance oral corticosteroids in patients with COPD and a history of severe and frequent exacerbations; and *6*) a conditional recommendation for opioid-based therapy in patients with COPD who experience advanced refractory dyspnea despite otherwise optimal therapy.

Conclusions: The task force made recommendations regarding the pharmacologic treatment of COPD based on currently available evidence. Additional research in populations that are underrepresented in clinical trials is needed, including studies in patients with COPD 80 years of age and older, those with multiple chronic health conditions, and those with a codiagnosis of COPD and asthma.

Keywords: COPD; exacerbation; dyspnea; steroids; pharmacotherapy

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This document has a related editorial.

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Summary of Recommendations

In patients with chronic obstructive pulmonary disease (COPD) who complain of dyspnea or exercise intolerance, we recommend long-acting β_2-agonist (LABA)/long-acting muscarinic antagonist (LAMA) combination therapy over LABA or LAMA monotherapy (strong recommendation, moderate certainty evidence).

In patients with COPD who complain of dyspnea or exercise intolerance despite dual therapy with LABA/LAMA, we suggest the use of triple therapy with inhaled corticosteroids (ICS)/LABA/LAMA over dual therapy with LABA/LAMA in those patients with a history of one or more exacerbations in the past year requiring antibiotics or oral steroids or hospitalization (conditional recommendation, moderate certainty evidence).

In patients with COPD who are receiving triple therapy (ICS/LABA/LAMA), we suggest that the ICS can be withdrawn if the patient has had no exacerbations in the past year (conditional recommendation, moderate certainty evidence).

We do not make a recommendation for or against ICS as an additive therapy to long-acting bronchodilators in patients with COPD and blood eosinophilia, except for those patients with a history of one or more exacerbations in the past year requiring antibiotics or oral steroids or hospitalization, for whom we suggest ICS as an additive therapy (conditional recommendation, moderate certainty evidence).

In patients with COPD and a history of severe and frequent exacerbations despite otherwise optimal therapy, we advise against the use of maintenance oral corticosteroid therapy (conditional recommendation, low certainty evidence).

In individuals with COPD who experience advanced refractory dyspnea despite otherwise optimal therapy, we suggest that opioid-based therapy be considered for dyspnea management, within a personalized shared decision-making approach (conditional recommendation, very low certainty evidence).

Introduction

The Global Initiative for Chronic Obstructive Lung Disease 2019 report defines COPD as a "common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway or alveolar abnormalities, usually caused by significant exposure to noxious particles or gases" (1). Pharmacologic treatment for COPD aims to improve quality of life (QOL) and control symptoms while reducing the frequency of exacerbations.

The purpose of this clinical practice guideline is to address specific clinically important questions regarding the pharmacologic management of COPD. The expert panel, in collaboration with a team of methodologists, prioritized and developed six questions that addressed significant COPD management issues. The panel used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach (*see* Table 1) (2, 3) to develop clinical recommendations.

The target audience for this guideline includes specialists in respiratory medicine. However, primary care physicians, internists, other healthcare professionals, patients, and policy makers may also find benefit from these recommendations. Although the panel used a systematic approach and the best available evidence to develop this guideline, it is important to note that study participants in many clinical trials may not reflect all populations. Specifically, patients older than 80 years, those with multiple chronic conditions, and those with a codiagnosis of COPD and asthma are rarely represented in clinical trials. We recommend that for all clinical management decisions, the patient and the healthcare provider should engage in a shared decision-making process.

Methods

The methodology applied in the development of this document with regard to formulating questions, rating the important outcomes, selecting studies, and synthesizing, formulating, and grading the evidence is described in detail in the online supplement. For all outcomes reporting standardized mean differences (SMDs), we used a default threshold of 0.50 for the SMD

point estimate to describe a meaningful clinically important difference (MCID) (4). A summary of the recommendations can be found in Table 2.

Results

Question 1: In Patients with COPD Who Complain of Dyspnea or Exercise Intolerance, Is LABA/LAMA Combination Therapy More Effective than and as Safe as LABA or LAMA Monotherapy?

Recommendation. For patients with COPD who complain of dyspnea or exercise intolerance, we recommend LABA/LAMA combination therapy over LABA or LAMA monotherapy (strong recommendation, moderate certainty evidence).

Critical outcomes. Outcome prioritization by the panel resulted in ranking hospital admissions, dyspnea, exacerbations, health-related QOL, and treatment-related adverse events as critical outcomes.

Summary of the evidence. The screeners identified 24 RCTs for final review inclusion ($N = 45{,}411$) (5–28).

Dyspnea score: Transition Dyspnea Index or COPD Assessment Test. Eleven studies ($n = 17{,}650$) assessed dyspnea (5, 6, 10, 15, 17, 19, 20, 22, 25–27). The panel acknowledged that the COPD Assessment Test provides a broader estimate of health status; however, one of its core components is dyspnea. The studies revealed an increased score (less breathlessness) in patients randomized to dual LABA/LAMA therapy versus monotherapy (SMD = 0.10; 95% confidence interval [CI], 0.07–0.13; $P < 0.001$), although this does not reach the MCID threshold.

Exacerbations. Fifteen studies ($n = 22{,}733$) assessed exacerbation risk (5, 6, 9, 10, 12–14, 17, 19–23, 26, 27). The studies revealed a reduced risk with the dual LABA/LAMA therapy versus monotherapy (risk ratio [RR], 0.80; 95% CI, 0.69–0.92; $P = 0.002$). There was moderate certainty in estimates of effect based on GRADE (absolute risk effect was 88 fewer per 1,000 patients; 95% CI, 136 fewer to 35 fewer).

Health-related QOL: Chronic Respiratory Disease Questionnaire or St. George's Respiratory Questionnaire. Eleven studies ($n = 18{,}897$) assessed health-related QOL (5, 10, 11, 14–18, 22, 24, 25). The studies revealed a reduced score (improved QOL) favoring dual LABA/LAMA therapy versus monotherapy (SMD = −0.13; 95% CI, −0.16 to −0.10; $P < 0.001$), although this does not reach the MCID threshold.

Hospital admissions. Three studies ($n = 9{,}719$) assessed risk of hospital admission (10, 19, 26). The studies revealed a reduced risk with dual LABA/LAMA therapy versus monotherapy (RR, 0.89; 95% CI, 0.82–0.97; $P = 0.01$) There was high certainty in estimates of effect based on GRADE (absolute risk effect was 19 fewer hospital admissions per 1,000 patients treated with LABA/LAMA as opposed to monotherapy; 95% CI, 32 fewer to 5 fewer).

Treatment-related adverse events. Twenty-three studies ($n = 38{,}758$) assessed treatment-related adverse events (5–17, 19–28). The studies revealed no significant difference in risk of treatment-related adverse events with dual LABA/LAMA therapy versus monotherapy (RR, 0.99; 95% CI, 0.97–1.01; $P = 0.34$).

Summary. Based on the five critical outcomes and completion of the GRADE evidence table, the overall certainty of evidence was judged to be "moderate."

Committee discussion. The panel noted a statistically significant decrease in exacerbations and hospital admissions in patients receiving dual therapy as opposed to monotherapy. The evidence also showed statistically significant improvements in dyspnea and QOL with dual therapy, although these did not reach the MCID

Table 1. Implications of Strong and Conditional Recommendations: From the Grading of Recommendations, Assessment, Development and Evaluation Working Group

	Strong Recommendation ("We recommend . . .")	Conditional Recommendation ("We suggest . . .")
For patients	The overwhelming majority of individuals in this situation would want the recommended course of action, and only a small minority would not. *(It is the right course of action for >95% of patients.)*	The majority of individuals in this situation would want the suggested course of action, but a sizable minority would not. *(It is the right course of action for >50% of patients.)*
For clinicians	The overwhelming majority of individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences. *(It is reasonable to recommend it strongly to patients and caregivers.)*	Different choices will be appropriate for different patients, and the clinician must help each patient arrive at a management decision consistent with her or his values and preferences. Decision aids may be useful to help individuals make decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working toward a decision. *(Slow down, think about it, discuss it with the patient.)*
For policy makers	The recommendation can be adopted as policy in most situations, including for use as a performance indicator. *(The recommended course of action may be an appropriate performance measure.)*	Policy making will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Performance indicators would have to focus on the fact that adequate deliberation about the management options has taken place. *(The recommended course of action is not appropriate for a performance measure.)*

threshold. In addition, the available studies did not reveal any evidence of harm with dual therapy compared with monotherapy. Given the above evidence, we believe that patients would thus opt for dual therapy over monotherapy.

Question 2: In Patients with COPD Who Complain of Dyspnea or Exercise Intolerance despite the Use of Dual Therapy with LABA/LAMA, Is Triple Therapy with ICS/LABA/LAMA More Effective than and as Safe as Dual Therapy with LABA/LAMA?

Recommendation. In patients with COPD who complain of dyspnea or exercise intolerance despite dual therapy with LABA/LAMA, we suggest the use of triple therapy with ICS/LABA/LAMA over dual therapy with LABA/LAMA in those patients with a history of one or more exacerbations in the past year requiring antibiotics or oral steroids or hospitalization (conditional recommendation, moderate certainty evidence).

Critical outcomes. Outcome prioritization by the panel resulted in ranking pneumonia, hospital admissions, exacerbations, ICU admissions, dyspnea, and health-related QOL as critical outcomes.

Subgroup analysis. A subgroup analysis was done based on patients with a history of one or more COPD exacerbations in the past year requiring treatment with antibiotics or oral steroids or hospitalization versus patients with zero to less than one exacerbation in the past year requiring treatment with antibiotics or oral steroids or hospitalization.

Summary of the evidence. The screeners identified four RCTs for final review inclusion ($n = 9{,}313$). Three of the four studies enrolled patients with a history of one or more exacerbations per year (19, 29, 30). In one study, patients were not required to have had an exacerbation in the past year (31).

Pneumonia. Three studies ($n = 8{,}964$) assessed incidence of pneumonia (29–31). The studies revealed a significantly increased risk of pneumonia with triple therapy as compared with dual therapy (rate ratio, 1.39; 95% CI, 1.02–1.90; $P = 0.03$). There was a high certainty in estimates of effect based on GRADE (absolute risk effect was 15 more pneumonias per 1,000 patients; 95% CI, 1 more to 35 more). The χ^2 interaction test suggested similar effects in frequency of pneumonia for those with a history of one or more exacerbations in the past year and those with zero to less than one exacerbation in the past year ($P = 0.74$).

Hospital admissions. One study ($n = 293$) evaluated the risk of all-cause hospital admissions (19). The study revealed no significant difference in risk of hospital admission with triple therapy as compared with dual therapy (rate ratio, 0.87; 95% CI, 0.62–1.24; $P = 0.44$). There was moderate certainty in estimates of effect based on GRADE (absolute risk effect was 42 fewer per 1,000 patients; 95% CI, 123 fewer to 78 more). There were no subgroups available to analyze.

Exacerbations. Four studies ($n = 9{,}257$) evaluated the risk of COPD exacerbations (19, 29–31). The studies revealed a significantly decreased risk of exacerbations with triple therapy as compared with dual therapy with LABA/LAMA (rate ratio, 0.71; 95% CI, 0.59–0.86; $P < 0.001$). There was moderate certainty in estimates of effect based on GRADE (absolute risk effect was 64 fewer exacerbations per 1,000 patients; 95% CI, 90 fewer to 31 fewer). The χ^2 interaction test suggested different effects in frequency of exacerbations for those with a history of one or more exacerbations in the past year and those with zero to less than one exacerbation in the past year ($P < 0.001$).

Subgroup with a history of one or more exacerbations in the past year. Three studies ($n = 7{,}993$) evaluated the risk of COPD exacerbations in subjects with a history of one or more exacerbations in the past year (19, 29, 30). The studies revealed a significantly decreased risk of exacerbations with triple therapy as compared with dual therapy with LABA/LAMA (rate ratio, 0.77; 95% CI, 0.72–0.81; $P < 0.001$). Assuming a baseline risk of COPD exacerbation in this subgroup of 1.0 exacerbations per patient per year, the absolute risk effect was 230 fewer exacerbations per 1,000 patients (95% CI, 280 fewer to 190 fewer).

Subgroup with zero to less than one exacerbation in the past year. One study ($n = 1{,}264$) revealed a significant reduction in the rate of exacerbations with triple therapy as compared with dual therapy with LABA/LAMA (rate ratio, 0.48; 95% CI, 0.37–0.62; $P < 0.001$) (31). Assuming a baseline risk of COPD exacerbation in this subgroup of 0.35 exacerbations per patient per year, the absolute risk difference/risk effect was 182 fewer exacerbations per 1,000 patients (95% CI, 220 fewer to 133 fewer).

ICU admissions. ICU admissions were not reported.

Dyspnea score: Transition Dyspnea Index. Two studies ($n = 1{,}494$) assessed dyspnea (19, 31). The studies revealed no significant change in dyspnea in patients treated with triple therapy as compared with dual therapy (MD = 0.20; 95% CI, −0.04 to 0.44; $P = 0.11$), and this does not reach the MCID threshold of 1 Transition Dyspnea Index (TDI) unit. The χ^2 interaction test suggested similar effects for subjects with and without exacerbations ($P = 0.58$).

Health-related QOL: St. George's Respiratory Questionnaire. Three studies ($n = 6{,}292$) assessed QOL (29, 31). The studies revealed a significantly lower score (improved QOL) favoring triple therapy over dual therapy (MD = −1.56; 95% CI, −2.39 to −0.74; $P < 0.001$); however, this does not exceed the MCID threshold for a St. George's Respiratory Questionnaire (SGRQ) score of −4 units. The χ^2 interaction test suggested similar effects in QOL for subjects with and without exacerbations ($P = 0.81$).

Summary. Based on the five critical outcomes and completion of the GRADE evidence table, the overall certainty of evidence was judged to be "moderate."

Committee discussion. The panel concluded that the benefits of triple therapy with ICS/LABA/LAMA outweigh the risks as compared with treatment with LABA/LAMA dual therapy in patients with COPD who complain of dyspnea or exercise intolerance despite dual therapy and have experienced one or more exacerbations in the past year. The panel noted that in three studies that randomized symptomatic patients with COPD and a history of exacerbations, the benefits of triple therapy in protecting against the risk of future exacerbations outweighed the increased risk of pneumonia. In these patients, the 23% rate reduction in exacerbations was believed to outweigh the 39% increased rate of pneumonia, as exacerbation events are much more common than pneumonia events in these patients. This was confirmed when the absolute risk differences were examined. Patients treated

Table 2. Population, Intervention, Comparator, and Outcomes Questions and Recommendations for the Pharmacologic Treatment of Stable Chronic Obstructive Pulmonary Disease

PICO Question	Recommendation	Strength of Recommendation	Certainty of Evidence
1. In patients with COPD who complain of dyspnea or exercise intolerance, is LABA/LAMA combination therapy more effective than and as safe as LABA or LAMA monotherapy?	In patients with COPD who complain of dyspnea or exercise intolerance, we recommend LABA/LAMA combination therapy over LABA or LAMA monotherapy.	Strong	Moderate certainty
2. In patients with COPD who complain of dyspnea or exercise intolerance despite the use of dual therapy with LABA/LAMA, is triple therapy with ICS/LABA/LAMA more effective than and as safe as dual therapy with LABA/LAMA?	In patients with COPD who complain of dyspnea or exercise intolerance despite dual therapy with LABA/LAMA, we suggest the use of triple therapy with ICS/LABA/LAMA over dual therapy with LABA/LAMA in those patients with a history of one or more exacerbations in the past year requiring antibiotics or oral steroids or hospitalization.	Conditional	Moderate certainty
3. In patients with COPD who are receiving triple therapy (ICS/LABA/LAMA), should the ICS be withdrawn?	In patients with COPD who are receiving triple therapy (ICS/LABA/LAMA), we suggest that the ICS can be withdrawn if the patient has had no exacerbations in the past year.	Conditional	Moderate certainty
4. In patients with COPD and blood eosinophilia, should treatment include an ICS in addition to a long-acting bronchodilator?	We do not make a recommendation for or against ICS as an additive therapy to long-acting bronchodilators in patients with COPD and blood eosinophilia, except for those patients with a history of one or more exacerbations in the past year requiring antibiotics or oral steroids or hospitalization, for whom we suggest ICS as an additive therapy.	Conditional	Moderate certainty
5. In patients with COPD who have a history of severe and frequent exacerbations despite otherwise optimal therapy, is maintenance oral steroid therapy more effective than and as safe as no maintenance oral steroid therapy?	In patients with COPD and a history of severe and frequent exacerbations despite otherwise optimal therapy, we advise against the use of maintenance oral corticosteroid therapy.	Conditional	Low certainty
6. In patients with COPD who experience advanced refractory dyspnea despite otherwise optimal therapy, is opioid-based therapy more effective than and as safe as no additional therapy?	In individuals with COPD who experience advanced refractory dyspnea despite otherwise optimal therapy, we suggest that opioid-based therapy be considered for dyspnea management, within a personalized shared decision-making approach.	Conditional	Very low certainty

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroids; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist; PICO = Population, Intervention, Comparator, and Outcomes.

with triple therapy experienced 15 more pneumonias per 1,000 patients; however, they also experienced 230 fewer COPD exacerbations per 1,000 patients. Thus, the panel concluded that for patients with COPD and a history of exacerbations, the benefits of triple therapy outweigh the risks.

However, the panel concluded that the benefits of triple therapy do not clearly outweigh the risks as compared with treatment with dual therapy in patients with COPD who have experienced zero to less than one exacerbation in the past year, because only one clinical trial was available that assessed this specific subgroup. In that study, these patients had a 39% increased relative risk of pneumonia and a 52% relative risk reduction in exacerbations. Patients treated with triple therapy experienced 15 more pneumonias per 1,000 patients, and 182 fewer COPD exacerbations per 1,000 patients. Although the data from this study suggest that these patients may benefit from triple therapy, the panel believed that additional studies are needed before triple therapy can be recommended for this subgroup.

Question 3: In Patients with COPD Who Are Taking Triple Therapy (ICS/LABA/LAMA), Should the ICS Be Withdrawn?

Recommendation. In patients with COPD who are receiving triple therapy with

ICS/LABA/LAMA, we suggest that the ICS can be withdrawn if the patient has had no exacerbations in the past year (conditional recommendation, moderate certainty evidence).

Subgroup analysis. A subgroup analysis was done for the exacerbation outcome based on patients with a history of one or more COPD exacerbations in the past year requiring treatment with antibiotics or oral steroids or hospitalization versus patients with no exacerbation in the past year requiring treatment with antibiotics or oral steroids or hospitalization.

Critical outcomes. Outcome prioritization by the panel resulted in ranking pneumonia, hospital admissions, exacerbations, all-cause death, ICU admissions, dyspnea, health-related QOL, and physical activity as critical outcomes.

Summary of the evidence. The screeners identified three RCTs for final review inclusion; however, one of the three studies was a subgroup analysis (32) of a larger trial (33), and thus only two studies were included for review ($n = 3{,}538$) (33, 34).

Pneumonia. Two studies ($n = 3{,}538$) assessed incidence of pneumonia (33, 34). The studies revealed no significant difference in risk of pneumonia with withdrawal of ICS and subsequent dual therapy as compared with triple therapy (RR, 0.92; 95% CI, 0.67–1.25; $P = 0.58$). There was moderate certainty in estimates of effect based on GRADE (absolute risk effect was 4 fewer pneumonias per 1,000 patients; 95% CI, 15 fewer to 11 more).

Hospital admissions. One study ($n = 2{,}485$) evaluated hospital admissions (33). The study revealed no significant difference in hospital admission with withdrawal of ICS and subsequent dual therapy as compared with continued triple therapy (RR, 0.99; 95% CI, 0.86–1.15; $P = 0.93$). There was moderate certainty in estimates of effect based on GRADE (absolute risk effect was 2 fewer admissions per 1,000 patients; 95% CI, 31 fewer to 33 more).

Exacerbations. Two studies ($n = 3{,}538$) evaluated the risk of COPD exacerbations (33, 34). The studies revealed no significant difference in risk of exacerbations with withdrawal of ICS and subsequent dual therapy as compared with continued triple therapy (rate ratio, 1.07; 95% CI, 0.97–1.17; $P = 0.17$). There was moderate certainty in estimates of effect based on GRADE (absolute effect was 15 more exacerbation events per 1,000 patients; 95% CI, 7 fewer to 37 more). The χ^2 interaction test suggested similar effects for the risk of COPD exacerbations for those with one or more exacerbations in the past year and those without a history of exacerbations ($P = 0.88$).

All-cause mortality. Two studies ($n = 3{,}538$) evaluated all-cause mortality (33, 34). The studies revealed no significant difference in risk of death with withdrawal of ICS and subsequent dual therapy as compared with continued triple therapy (RR, 1.09; 95% CI, 0.73–1.65; $P = 0.66$). There was moderate certainty in estimates of effect based on GRADE (absolute risk effect was two more deaths per 1,000 patients; 95% CI, seven fewer to one more).

ICU admissions. ICU admissions were not reported.

Dyspnea scores. Information regarding dyspnea scores was not complete and could not be pooled.

Health-related QOL: SGRQ. Two studies ($n = 3{,}538$) assessed QOL (33, 34). The studies showed a significant decrease in QOL (increased SGRQ score) between withdrawal of ICS versus continued triple therapy (MD = 1.22; 95% CI, 1.15–1.29; $P < 0.0001$); however, this does not exceed the MCID threshold for an SGRQ score of 4 units.

Physical activity. Physical activity was not reported.

Summary. Based on the six critical outcomes and completion of the GRADE evidence table, the overall certainty of evidence was judged to be "moderate."

Committee discussion. According to the available evidence, withdrawal of ICS was not associated with a statistically significant difference in risk of pneumonia, all-cause mortality, or risk of COPD exacerbation. The change in QOL did not exceed the MCID threshold. Given the paucity of evidence, and hence the inability to confirm the risks and benefits associated with withdrawal of ICS from triple therapy, and in light of the analysis of data from Population, Intervention, Comparator, and Outcomes (PICO) question 2, which showed that triple therapy is of benefit in patients with a history of exacerbations, the panel suggests that ICS can be withdrawn and patients can be converted from triple therapy to dual therapy with LABA/LAMA if there is no history of exacerbations in the past year.

Question 4: In Patients with COPD and Blood Eosinophilia, Should Treatment Include an ICS in Addition to a Long-Acting Bronchodilator?

Recommendation. We do not make a recommendation for or against ICS as an additive therapy to long-acting bronchodilators in patients with COPD and blood eosinophilia (defined as ⩾2% blood eosinophils, or ⩾150 cells/μl), except for those patients with a history of one or more exacerbations in the past year requiring antibiotics or oral steroids or hospitalization, for whom we suggest ICS as an additive therapy (conditional recommendation, moderate certainty evidence).

Critical outcomes. Outcome prioritization by the panel resulted in ranking pneumonia, hospital admissions, exacerbations, dyspnea, and health-related QOL as critical outcomes.

Summary of the evidence. The screeners identified eight RCTs ($n = 9{,}123$) (30, 31, 35–40). The chosen thresholds for the percentage of eosinophils in blood (⩾2% eosinophils) and the number of eosinophils per microliter of blood (⩾150) were based on the values presented in the studies analyzed for the review.

Pneumonia (⩾2% eosinophils). Two studies ($n = 4{,}131$) assessed incidence of pneumonia in patients with ⩾2% blood eosinophils (35, 38). The studies revealed an increased risk of pneumonia with an ICS in addition to a long-acting bronchodilator (RR, 1.99; 95% CI, 1.31–3.00; $P = 0.001$). There was moderate certainty in estimates of effect based on GRADE (absolute risk effect was 26 more pneumonias per 1,000 patients; 95% CI, 8 more to 52 more).

Pneumonia (⩾150 eosinophils). Two studies ($n = 4{,}267$) assessed incidence of pneumonia in patients with ⩾150 blood eosinophils/μl (36, 38). The studies revealed an increased risk of pneumonia with an ICS in addition to a long-acting bronchodilator (RR, 1.55; 95% CI, 1.23–1.95; $P < 0.001$). There was moderate certainty in estimates of effect based on GRADE (absolute risk effect was 44 more

pneumonias per 1,000 patients; 95% CI, 18 more to 76 more).

Hospital admissions. Hospital admissions were not reported.

Exacerbations (≥2% eosinophils). Six studies ($n = 5,517$) assessed rates of COPD exacerbations in patients with ≥2% blood eosinophils (30, 35, 37–40). The studies revealed a reduced risk of exacerbations with an ICS in addition to a long-acting bronchodilator versus a long-acting bronchodilator alone (rate ratio, 0.78; 95% CI, 0.67–0.92; $P = 0.004$). There was moderate certainty in estimates of effect based on GRADE. Assuming a baseline risk of COPD exacerbation in this subgroup of one exacerbation per patient per year, the absolute risk effect was 209 fewer exacerbations per 1,000 patients (95% CI, 313 fewer to 76 fewer).

Exacerbations (≥150 eosinophils/μl). Six studies ($n = 8,106$) assessed rates of COPD exacerbations in patients with ≥150 blood eosinophils/μl (30, 31, 36, 38–40). The studies revealed a reduced risk of exacerbations with an ICS in addition to a long-acting bronchodilator versus a long-acting bronchodilator alone (rate ratio, 0.70; 95% CI, 0.59–0.84; $P < 0.001$). There was moderate certainty in estimates of effect based on GRADE. Assuming a baseline risk of COPD exacerbation in this subgroup of one exacerbation per patient per year, the absolute risk effect was 285 fewer exacerbations per 1,000 patients (95% CI, 390 fewer to 152 fewer).

Dyspnea score: TDI (≥150 eosinophils/μl). One study ($n = 4,269$) assessed dyspnea in patients with ≥200 blood eosinophils/μl (36). The study revealed no significant difference in dyspnea with an ICS in addition to a long-acting bronchodilator versus a long-acting bronchodilator alone (MD = 0.16; 95% CI, −0.15 to 0.47; $P = 0.31$), and this does not reach the MCID threshold for a TDI of 1 unit.

Health-related QOL: SGRQ (≥150 eosinophils/μl). Two studies assessed QOL ($n = 4,762$) (36, 39). The studies revealed a statistically improved QOL with an ICS in addition to a long-acting bronchodilator versus a long-acting bronchodilator alone (MD = −2.31 units; 95% CI, −3.83 to −0.78; $P = 0.003$); however, this does not exceed the MCID threshold for an SGRQ score of −4 units.

Summary. Based on the five critical outcomes and completion of the GRADE evidence table, the overall certainty of evidence was judged to be "moderate."

Committee discussion. According to the available evidence, the addition of ICS to a long-acting bronchodilator in patients with COPD and blood eosinophilia was associated with a significantly increased risk of pneumonia and a significantly decreased risk of exacerbations. Patients with blood eosinophilia treated with ICS plus a long-acting bronchodilator experienced 26–44 more pneumonias per 1,000 patients and 209–285 fewer COPD exacerbations per 1,000 patients.

However, the panel recognized that the studies included within this PICO question analyzed the effects of ICS and a long-acting bronchodilator in patients with elevated blood eosinophils as subgroup analyses, which in many cases were performed *post hoc*. In addition, nonstandardized thresholds were used in the various studies to define "eosinophilia." Thus, the panel believed the quality of the available studies was not optimal, and hence the committee was reluctant to recommend ICS for all patients with COPD and blood eosinophilia. However, given the weight of the evidence presented for PICO question 2, which shows that ICS are beneficial in patients with a history of exacerbations, the panel believed that patients with blood eosinophilia and a history of exacerbations would likewise benefit from the addition of ICS to a long-acting bronchodilator.

Question 5: In Patients with COPD Who Have a History of Severe and Frequent Exacerbations despite Otherwise Optimal Therapy, Is Maintenance Oral Steroid Therapy More Effective than and as Safe as No Maintenance Oral Steroid Therapy?

Recommendation. In patients with COPD and a history of severe and frequent exacerbations despite otherwise optimal therapy, we advise against the use of maintenance oral corticosteroid therapy (conditional recommendation, low certainty evidence).

Critical outcomes. Outcome prioritization by the panel resulted in ranking mortality, exacerbations, dyspnea, hospital admissions, bone fractures, QOL, and treatment-emergent adverse events as critical outcomes.

Summary of the evidence. The screeners identified four RCTs ($n = 477$) (41–44).

Mortality. Two studies ($n = 241$) assessed mortality risk (41, 42). The studies revealed no significant difference in mortality with the use of oral steroid versus no oral steroid (RR, 1.01; 95% CI, 0.28–3.70; $P = 0.98$). There was moderate certainty in estimates of effect based on GRADE (absolute risk effect was 0 fewer per 1,000 patients; 95% CI, 26 fewer to 98 more).

Exacerbations. Two studies ($n = 108$) assessed exacerbation risk (42, 43). The studies revealed no significant difference in exacerbations with the use of maintenance oral steroid versus no oral steroid (RR, 1.38; 95% CI, 0.90–2.10; $P = 0.14$). There was moderate certainty in estimates of effect based on GRADE (absolute risk effect was 190 more per 1,000 patients; 95% CI, 50 fewer to 550 more).

Dyspnea (daily symptom score, visual analog scale). Two studies ($n = 142$) assessed dyspnea (42, 44). The studies revealed no statistically significant difference in dyspnea with the use of maintenance oral steroids versus no oral steroids (SMD = −0.22; 95% CI, −0.56 to 0.12; $P = 0.21$).

Hospital admissions. One study ($n = 191$) assessed the risk of hospital admission (41). The study revealed no significant difference in admissions with the use of oral steroids versus no oral steroids (RR, 0.64; 95% CI, 0.25–1.61; $P = 0.34$). There was moderate certainty in estimates of effect based on GRADE (absolute risk effect was 42 fewer per 1,000 patients; 95% CI, 88 fewer to 71 more).

Treatment-emergent adverse events. Two studies ($n = 247$) assessed treatment-emergent adverse events (41, 42). The studies revealed a statistically significant increased risk of adverse events with oral steroid use versus no oral steroids (RR, 1.65; 95% CI, 1.16–2.34; $P = 0.006$). There was low certainty in estimates of effect based on GRADE (absolute risk effect was 174 more per 1,000 patients; 95% CI, 43 more to 359 more).

Summary. Based on the five critical outcomes using RCT evidence and completion of the GRADE evidence table, the overall certainty of evidence was judged to be "low."

Committee discussion. The panel believed that maintenance oral steroid therapy has not been shown to improve clinical outcomes, and the available evidence suggests that chronic oral steroid therapy has a potential for harm. Two RCTs revealed an increased risk of adverse events with oral steroid use, suggesting excess harms to patients who are prescribed daily oral steroids. However, this recommendation was based on RCTs with small sample sizes, a small number of events, short durations, and broad CIs around the point estimates. In addition, these studies were done when there was a paucity of medications available for maintenance therapy. The quality of the underlying evidence was poor, and therefore the panel believed that a recommendation in favor of maintenance oral steroid use would be problematic given the concerns surrounding patient safety. The panel also believed that well-informed patients would place a higher value on avoiding the potential harms of adverse events and less value on the uncertain benefits of decreased dyspnea and hospital admissions.

Question 6: In Patients with COPD Who Experience Advanced Refractory Dyspnea despite Otherwise Optimal Therapy, Is Opioid-based Therapy More Effective than and as Safe as No Additional Therapy?

Recommendation. In individuals with COPD who experience advanced refractory dyspnea despite otherwise optimal therapy, we suggest that opioid-based therapy be considered for dyspnea management within a personalized shared decision-making approach (conditional recommendation, very low certainty evidence).

Critical outcomes. Outcome prioritization by the panel resulted in ranking emergency department visits, dyspnea, exacerbations, health-related QOL, falls/accidents, overdose, and exercise capacity as critical outcomes.

Summary of the evidence. The screeners identified 14 RCTs for final review inclusion ($n = 366$) (45–58).

Exacerbations. One study ($n = 30$) assessed exacerbation risk (52). The study revealed no significant difference in exacerbations between the opioid and no-opioid groups (RR, 1.38; 95% CI, 0.74–2.55; $P = 0.31$). There was low certainty in estimates of effect based on GRADE (absolute risk effect was 190 more exacerbations per 1,000 patients; 95% CI, 130 fewer to 775 more).

Emergency department visits. One study ($n = 30$) assessed the risk of emergency department visits (52). The study revealed no significant difference in risk between the opioid and no-opioid groups (RR, 4.41; 95% CI, 0.23–84.79; $P = 0.33$). There was low certainty in estimates of effect based on GRADE (absolute risk effect was125 more admissions per 1,000 patients; 95% CI, 66 fewer to 316 more per 1,000 patients).

Falls/accidents. One study ($n = 38$) with a small sample size assessed the risk of falls/accidents (46). The study revealed no significant difference in risk of falls between the opioid and no-opioid groups (RR, 0.37; 95% CI, 0.02–8.51; $P = 0.53$). There was low certainty in estimates of effect based on GRADE (absolute risk effect was 32 fewer per 1,000 patients; 95% CI, 49 fewer to 376 more).

Overdose. One study ($n = 38$) assessed the risk of overdose/oversedation (46). The study revealed no significant difference in risk between the opioid and no-opioid groups (RR, 3.32; 95% CI, 0.14–76.6; $P = 0.45$). There was low certainty in estimates of effect based on GRADE (absolute risk effect was 56 more per 1,000 patients; 95% CI, 82 fewer overdoses per 1,000 patients to 193 more per 1,000 patients).

Health-related QOL: assessed using a visual analog scale. One study ($n = 40$) assessed health-related QOL (53). The study revealed a significant difference in the visual analog scale, with an increased score in the group that was randomized to opioids (MD = 1.50; 95% CI, 0.66–2.34; $P = 0.03$), indicating improved QOL.

Dyspnea: diary cards, visual analog scales, Medical Research Council scale, and Chronic Respiratory Disease Questionnaire dyspnea subscale. Twelve studies ($n = 240$) assessed dyspnea (45, 46, 48–53, 55–58). The studies revealed a significant difference in dyspnea, favoring the group that received opioids (SMD = −0.60; 95% CI, −1.08 to −0.13; $P = 0.01$), and this exceeds the MCID threshold. No subgroup differences were noted when systemic versus nebulized administration subgroups were analyzed ($P = 0.08$).

Exercise capacity. Nine studies ($n = 103$) assessed exercise capacity (45, 47, 48, 50–55, 57). The studies revealed no significant difference between the opioid and no-opioid groups (SMD = 0.14; 95% CI, −1.42 to 1.70; $P = 0.86$), and this does not reach the MCID threshold. No subgroup differences were noted when systemic versus nebulized administration subgroups were analyzed ($P = 0.10$).

Summary. Based on the eight critical outcomes and completion of the GRADE evidence table, the overall certainty of evidence was judged to be "very low."

Committee discussion. The panel noted that in patients with advanced refractory dyspnea, there was a statistically and clinically meaningful improvement in dyspnea with opioid treatment. The panel believed that a conditional recommendation in favor of opioid use was reasonable for dyspnea management given the accumulated evidence, and that well-informed patients might place a higher value on the improvement in dyspnea and less value on the uncertain harms of exacerbations, hospitalizations, falls, or overdoses. The panel believed that the observed benefit in dyspnea outweighed the uncertain risks. However, many of these studies were undertaken when there was a relative paucity of maintenance medications available to treat COPD, and the presumed effects of opioids might differ in today's clinical context. Therefore, given the very low certainty of evidence, the use of opioids must be evaluated by clinicians and patients in a shared decision-making process.

Conclusions

In developing this guideline, we performed a rigorous, PICO-driven distillation of the scientific evidence to provide recommendations pertaining to key questions regarding the pharmacologic treatment of COPD. We hope that clinicians and researchers will find this guideline useful; however, it is important to apply these recommendations along with clinical assessments and shared decision-making to ensure that patients receive optimal clinical care. We also recognize that slowing the progression of disease and improving mortality are important goals of therapy; however, pharmacotherapy has not definitely been proven to affect these outcomes.

Improvements in COPD mortality and disease progression have thus far only been achieved through smoking cessation.

The panel recognizes that there are limitations to this clinical practice guideline. The recommendations were based on the available scientific evidence. In many cases, the available clinical trials did not include certain COPD populations, such as patients over 80 years of age, those with chronic comorbid conditions, and those with COPD/asthma overlap. In addition, the available evidence did not risk stratify patients with exacerbations or those with eosinophilia. It is also important to note that the panel did not include patient representatives or family/caregiver representatives. Their participation might have been important in prioritizing clinical outcomes.

Many questions remain regarding the optimal pharmacologic therapy for patients with varying risks of exacerbations and levels of eosinophilia, as well as potentially different medication responses among current and former smokers. We hope that the research priorities outlined in this document will prompt new research to identify more specific patient profiles and enable personalized, patient-centered care. ■

This official guideline was prepared by an *ad hoc* subcommittee of the ATS Assembly on Clinical Problems.

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