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COPD 2024: APPLYING THE CANADIAN THORACIC SOCIETY (CTS) 2023 CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) GUIDELINE FOR PREVENTING EXACERBATIONS, IMPROVING HEALTH STATUS, AND PREVENTING MORTALITY

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a common, chronic respiratory condition that is associated with the risk of morbidity and mortality. Approximately 2 million Canadians live with COPD, and as many as 1 million suffer while remaining undiagnosed and untreated.[1] COPD exacerbations represent the most expensive cause of hospitalization with the highest likelihood of hospital readmission.[1]

Exacerbations are the primary driver of mortality in patients with COPD. These exacerbations are the second leading cause of hospitalization in Canada with an average length of stay of 7 days.[2] In fact, 1 in 5 patients with COPD will die within 1 year of their first hospitalization due to an exacerbation.[3] For those 65 or older in Ontario, the overall 365-day mortality stands at nearly 28% following their first hospitalization due to an exacerbation.[4] The best indicator of the risk of future exacerbations is a history of exacerbations.

The time has come to end the stepwise pharmacologic escalation that has defined the treatment paradigm in COPD. The call to action is to shift from the slow promotion of inhaled pharmacotherapy based on exacerbations to a direct escalation to inhaled pharmacotherapy with demonstrated evidence to prevent the exacerbations.

What Are The Risk Factors and The Burden of Disease?

COPD is a disease characterized by persistent airflow limitation. The etiology revolves around exposure to combustion byproducts. This involves individuals with exposure to tobacco and cannabis smoke. This exposure can occur through either personal smoking or via passive second hand exposure. As well, electronic cigarettes are a growing concern as an etiologic agent due to the increase in airway inflammation that may lead to the development of COPD. In addition, COPD can be attributed to chronic exposure to biomass fuels and air pollution.[5] Those with exposure to household indoor air pollution, and ambient air pollution, as well as those with outdoor smoke exposure, are at an increased risk for the development of underlying COPD. Patients without a personal tobacco history, yet presenting with dyspnea, should be asked about their exposure to indoor air pollution, ambient outdoor pollution, or biomass exposure.

What Are The Key Indicators For Considering a Diagnosis of COPD?

In addition to chronic exposure to an etiologic agent, key indicators for consideration for COPD include the following: dyspnea that is progressive over time, persistent, or is characteristically worse with exercise; chronic cough and sputum production that may be intermittent, and while the cough may be dry, it is usually associated with a productive sputum component; individuals with a recurrent wheeze; and those with recurrent lower respiratory tract infections.

The diagnostic test for confirmation of COPD is a post-bronchodilator spirometry test. In those with COPD, this test demonstrates that less than 70% of the air can be exhaled from the lungs in the first second, indicated by a Forced Expiratory Volume in 1 second (FEV1)/ Forced Vital Capacity (FVC) ratio of <0.7 and absence of significant bronchodilator response. The severity of COPD, as determined by spirometry, is defined by the percent predicted post-bronchodilator FEV1.

How Can We Screen and Diagnose COPD More Effectively And Earlier In a Primary Care Setting?

COPD is irreversible and progressive, yet it marches in a steady, insidious manner that may blend into the background of life. Symptoms associated with COPD are often misconstrued as related to aging, deconditioning, or the steady decline of functional status that occurs with the passage of time.

Active screening for symptomatic individuals at risk of COPD is required for an early diagnosis of the condition. The Canadian Lung Health Test is a validated screening

Do you cough regularly?
Do you cough up phlegm regularly?
Do even simple chores make you short of breath?
Do you wheeze when you exert yourself or at night?
Do you get frequent colds that persist longer than those of people you know?[6]

tool to identify patients with possible COPD by screening those who are aged 40 years or older and are either currently smoking or former smokers who have a minimum 10 pack-year tobacco history. If they answer yes to one of the following questions, it is recommended that they undergo screening for COPD with post-bronchodilator spirometry.

If a patient responds yes to one or more of the Canadian Lung Health Test questions, screening for COPD with post-bronchodilator spirometry is recommended. In an outpatient screening cohort, 26% of patients who screened positive with the Canadian Lung Health Test received a new diagnosis of COPD. In addition, 93% of those newly-diagnosed patients had mild or moderate disease, notably capturing those early in the disease course.[7]

Is The Goal Exacerbation Reduction or Symptom Control or Both?

The goals of therapy for COPD involve the alleviation of dyspnea, improvement of health status, and an improved quality of life (**Figure 1**).[8] The foundation of COPD management across the entire disease spectrum involves self-management education. This involves several key components, including optimization of inhaler technique; inhaler review and subsequent re-review; assessment and review of medication adherence; breathing and cough techniques; as well as an understanding and early recognition of acute exacerbations of COPD with a documented action plan and its implementation. Complete cessation of tobacco use, or inhaled smoke exposure is paramount to slow the progression of COPD. Tobacco cessation carries a mortality benefit. Physical activity with regular daily exercise is essential to promote overall health and well-being. The recommended vaccines for individuals with COPD include the COVID-19 primary series, Pneumococcal, Respiratory Syncytial Virus, Pertussis, and Herpes Zoster.[5]

Inhaled maintenance medications, in addition to preventative pharmacotherapy, are recommended for all patients with COPD across the entire disease spectrum, with the goal of alleviating the symptom burden with respect to dyspnea and exercise tolerance, thereby enhancing the overall health status. Inhaled pharmacotherapy is fundamental in preventing acute exacerbations of COPD and in reducing mortality.

How Can We Best Identify Those With COPD Whose Disease Is Not Under Good Control and When Should We Escalate Their Treatment?

The 2023 Canadian Thoracic Society (CTS) guideline on pharmacotherapy **(Figure 2)** in patients with stable COPD presents an organized, evidence-informed approach that aligns effective treatments based on symptom burden, spirometry, and the risk of future exacerbations and mortality.[8]

The first step toward identifying evidence-based inhaled pharmacotherapy involves an assessment of the patient's symptom burden, lung function, and risk of exacerbation and mortality.

When assessing the symptom burden, the COPD Assessment Test (CAT), a validated 8-question tool, is used to assess the impact of COPD as a major medical condition impacting the patient's quality of life **(Figure 3)**. The CAT assesses domains such as cough, sputum, chest tightness, exertional dyspnea, activity limitation, confidence leaving the home, quality of sleep, and energy level. A CAT score of 10 or higher places the patient on the higher-risk side of the CTS algorithm, indicating a more moderate and severe burden of disease.

If the CAT score is not available, the modified Medical Research Council (MRC) breathlessness scale is a validated instrument for the assessment of symptom burden in COPD **(Figure 4)**. The key discriminator is the modified MRC grade of 2 for dyspnea. An individual at an MRC grade of 2 for dyspnea would comment that on level ground they walk slower than people of the same age because of breathlessness or they have to stop when walking at their own pace because of dyspnea. The key cutoff is a modified MRC grade of 2 or higher, indicating worse dyspnea, which places the patient on the moderate to severe side of the algorithm.

Patients are then stratified based on lung function. Mild COPD with a spirometric post-bronchodilator FEV1 of greater than or equal to 80% places patients on the milder, left side of the CTS COPD algorithm **(Figure 2)**. However, those with moderate COPD, or worse, have an FEV1 of less than 80%, are placed on the moderate to severe side of the algorithm.

Finally, exacerbation of COPD and mortality risk are assessed with a retrospective assessment of exacerbations that have occurred in the previous year.

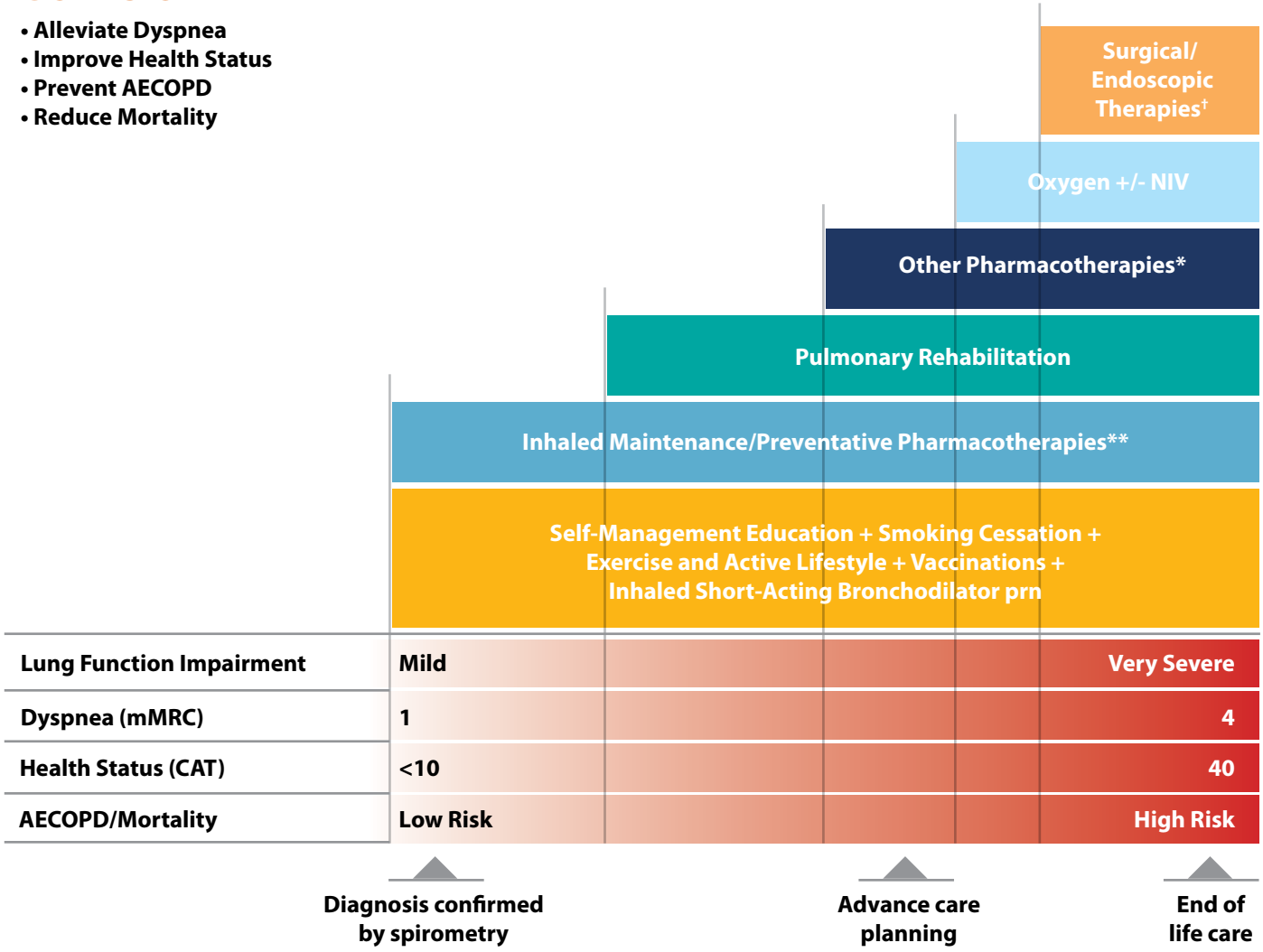

Figure 1. Integrated Comprehensive Management of COPD; *adapted from Bourbeau, J et al., 2023*

Integrated comprehensive management of COPD includes confirming COPD diagnosis with postbronchodilator spirometry, evaluation and on-going monitoring of dyspnea/symptom burden and risk of exacerbations and use of both pharmacologic and nonpharmacologic interventions (see Figure 3) to alleviate dyspnea/symptoms, improve health status, prevent AECOPD and reduce mortality. The approach should not be viewed as "stepwise" and may not necessarily occur in the order they appear for all patients. Self-Management Education includes optimizing inhaler device technique and [re-]review, assessment and review of medication adherence, breathing and cough techniques, early recognition of AECOPD, written AECOPD action plan and implementation (when appropriate), promoting physical activity and/or exercise, and other healthy habits including diet and smoking cessation.

† Surgical therapies may include lung transplantation and lung volume reduction (including with endoscopic valves).

* Other pharmacotherapies include oral therapies (prophylactic macrolide, and PDE-4 inhibitor, mucolytic agents for patients with chronic bronchitis), alpha-1-anti-trypsin augmentation therapy for documented severe A1AT deficiency, and opioids for severe refratory dyspnea (see prior CTS Guideline).

** Inhaled Maintenance/Preventative Pharmacotherapies are long-acting muscarinic antagonists (LAMA) and/or long-acting β2-antagonists (LABA) with or without inhaled corticosteroids (ICS). ICS montherapy should NOT be used in COPD management.

Abbreviations: A1AT= alpha-1 antrtrypsin; **AECOPD =** acute exacerbation of COPD; **CAT=** COPD assessment test; **COPD =** chronic obstructive pulmonary disease; **CTS =** Canadian Thoracic Society; **mMRC =** modified Medical Research Council; **prn =** as-needed; **NIV =** noninvasive ventilation.

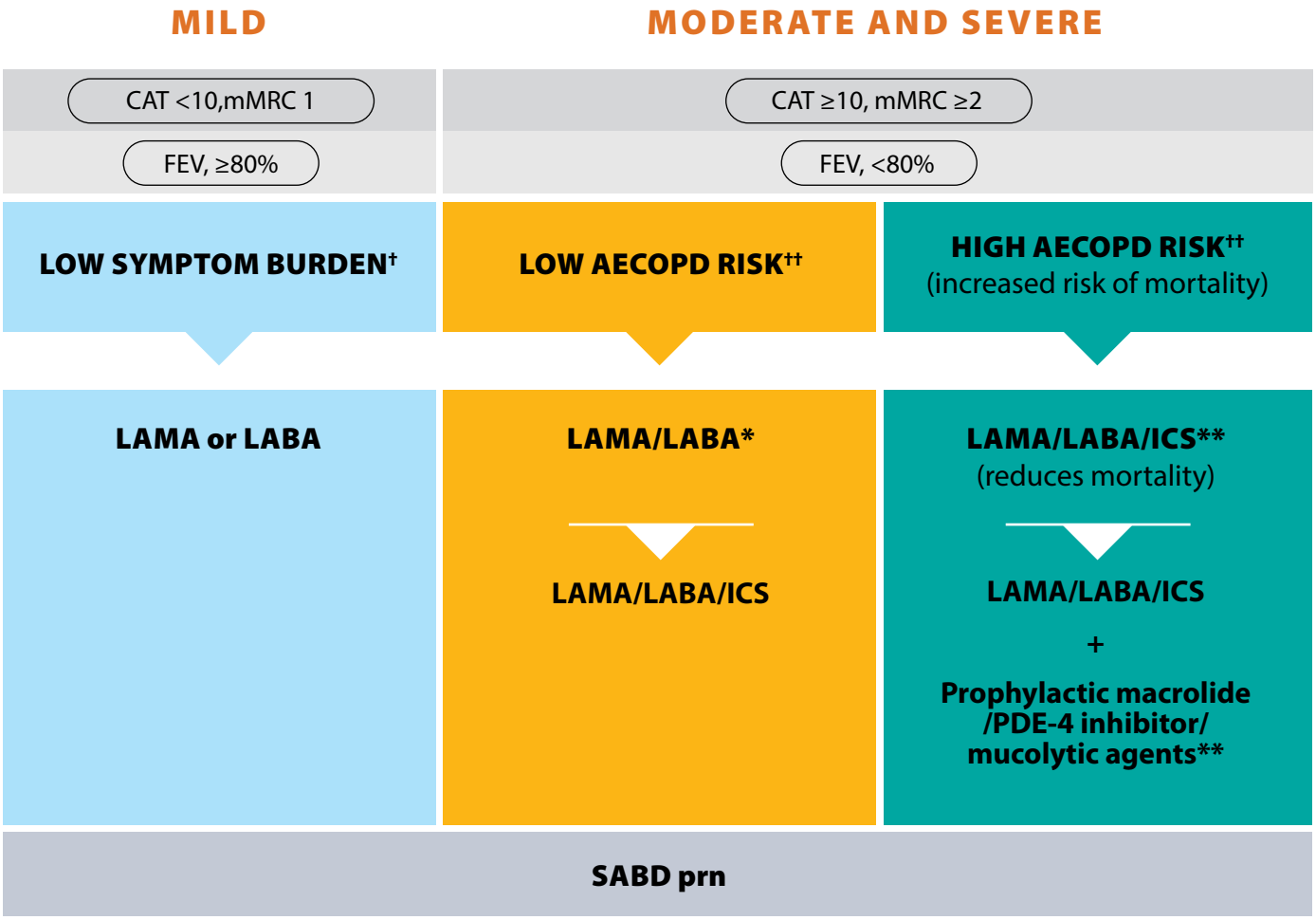

Figure 2. COPD Pharmacotherapy; *adapted from Bourbeau, J et al., 2023*

This figure promotes an evidence-informed approach that aligns proven effective treatments with spirometry, symptom burden, risk of future exacerbations and mortality risk. Because of the clinical heterogeneity in COPD, spirometry should not be used in isolation to assess disease severity and this is why it is also important to perform a thorough clinical evaluation of the patient, including symptom burden and risk of exacerbations that permits the implementations of treatments that are specific for subpopulations. SABD prn (as needed) should accompany all recommended therapies across the spectrum of COPD.

† Symptom burden encompasses shortness of breath, activity limitation, and impaired health status.

†† Individuals are considered at "Low Risk of AECOPD" if ≤1 moderate AECOPD in the last year (moderate AECOPD is an event with prescribed antibiotic and/or oral corticosteroids) and did not require hospital admission/ED visit).

* LAMA/LABA single inhaled dual therapy is preferred over ICS/LABA inhaled combination therpay considering the additional improvements in lung function and the lower rates of adverse events such as pneumonia. ISC/LABA combination therapy should be used in individuals with concomitant asthma. There is no universally accepted definition of concomitant asthma. The 2017 CTS Position Statement on COPD Pharmacotherapy provides guidance on the assessment of patients who may have concomitant asthma.

** Triple inhaled ICS/LAMA/LABA combination therapy should preferably be administered in a single inhaler triple therapy (SITT), and not in multiple inhalers (see text), although we acknowledge that some patients continue to prefer separate inhalers. *Oral pharmacotherapies in this group include prophylactic macrolide, and PDE-4 inhibitor and mucolytic agents for patients with chronic bronchitis.

Abbreviations: CAT = COPD assessment test; **mMRC =** Modified Medical Research Council; **SABD prn =** short-acting bronchodilator as needed; **AECOPD =** acute exacerbation of COPD; **ED =** emergency department; **LAMA =** long-acting muscarinic antagonist; **LABA =** long-acting β2-antagonist; **ICS =** inhaled corticosteroid.

These exacerbations are acute, trajectory-altering events in the life of a patient with COPD that are characterized by increasing dyspnea, sputum volume, sputum purulence, and symptom burden. In a patient with COPD, the term chest infection is a disservice; exacerbation of COPD is the appropriate descriptor. Mild COPD exacerbations are typically managed on an outpatient basis, and do not require escalation of maintenance inhaled therapy, yet they do require the use of a reliever medication, almost universally a short-acting beta agonist (SABA). Moderate COPD exacerbations require outpatient pharmacotherapy involving an oral corticosteroid alone or in combination with antibiotic therapy if there is an infectious exacerbation. Severe COPD exacerbations are defined as those requiring an emergency department visit or admission to hospital/ICU.

Those at low risk of acute exacerbations of COPD are those who, in the past year have had at most one moderate exacerbation that was managed on an outpatient basis and have not had a severe exacerbation. Those at high risk for exacerbation and mortality are those that have had 2 or more moderate exacerbations that were managed on an outpatient basis, or one or more severe exacerbations.

Fundamental to this algorithmic approach of pharmacotherapy in COPD is the recognition that higher-risk features take precedence over lower-risk features. An individual with a low symptom burden along with a high-risk exacerbation history would be defined within the algorithm by the higher-risk feature. The higher-risk features take precedence over the lower-risk features when proceeding through the algorithm to identify the appropriate COPD pharmacotherapy.

What About Mild COPD?

As mentioned previously, mild COPD is characterized by a spirometric post-bronchodilator FEV1 that is greater than or equal to 80% and a low symptom burden with a CAT

Figure 3. COPD Assessment Test; adapted from https://www.catestonline.org

score of less than 10 or a modified MRC grade of dyspnea of 0 to 1. While patients with mild COPD present with a low symptom burden and an absence of exacerbations, fundamentally they possess a fixed, chronic, progressive obstructive lung disease. The era of SABA-only therapy for mild COPD is over. SABA therapy is necessary for all patients across the spectrum of COPD; however, this therapy is insufficient. Patients with mild COPD should be placed on long-acting bronchodilator therapy with a long-acting muscarinic antagonist (LAMA) or a long-acting beta agonist (LABA). There is evidence that the use of LAMA therapy in early-stage COPD can attenuate the rate of decline of lung function and reduce the frequency of exacerbations.[9] Thus, the foundation of inhaled COPD therapy involves long-acting bronchodilator therapy, and those with mild disease deserve this therapy at a minimum.

What Is The Evidence For Dual Versus Triple Therapy?

In a patient population actively screened for COPD, close to 50% of patients will have moderate spirometric disease, and moderate or worse disease will constitute between 70 to 80% of patients.[10,11] Frequent exacerbations of 2 or more per year, will occur in approximately a quarter of patients. Nearly three-quarters of patients have infrequent exacerbations with at most 1 exacerbation in the previous year.[12]

Individuals with a low risk of acute exacerbations of COPD along with a moderate to high symptom burden, characterized by health status impairment with a CAT score of 10 or higher, or a modified MRC grade of 2 or higher for dyspnea, and a moderate or worse spirometric COPD, should be initiated on dual bronchodilator therapy.

The subset of individuals with symptomatic COPD and a moderate to high symptom burden, characterized by a modified MRC grade of 2 or higher for dyspnea, constitute a sizable proportion of patients seen in clinical practice.[13]

The foundation of management for this large subset of those with symptomatic yet infrequently exacerbating COPD is dual bronchodilator therapy. The CTS guideline places patients with moderate or worse spirometric disease and a high symptom burden characterized by the CAT or modified MRC in the centre of our algorithm for a good reason. The minimum therapy for symptomatic COPD with a high symptom burden or a moderate to worse spirometry-confirmed severity with infrequent exacerbations is dual bronchodilator therapy.

If dual bronchodilator therapy is insufficient for addressing the symptom burden, or if in the future this therapy becomes insufficient, or if an exacerbation occurs, patients should be escalated to single inhaler triple therapy. Compared to the previous iteration of our guidelines in 2019, the backward arrows permitting de-escalation of inhaled therapy have been removed.[14] Though this patient population may not experience frequent exacerbations, if dual bronchodilator therapy is insufficient for controlling the symptom burden, becomes insufficient, or an exacerbation occurs, escalation to triple therapy is recommended. The Kronos clinical trial, which included a significant proportion of patients (74%), who have not had an exacerbation in the previous year, demonstrated a lower likelihood of exacerbation for those on triple therapy versus those on dual bronchodilator therapy.[15]

Who Should Have Triple Therapy, and Why?

Your friendly neighbourhood Respirologist is likely a frequent prescriber of single inhaler triple therapy in COPD, but this is expected given the severity of patients they co-manage with primary care. With only approximately a quarter of COPD patients experiencing frequent exacerbations,[12] triple therapy is reserved for those for whom dual bronchodilator therapy is insufficient at managing their symptoms, or if they have experienced

Grade	Description of breathlessness
0	I only get breathless with strenuous exercise
1	I get short of breath when hurrying on level ground or walking up a slight hill
2	On level ground, I walk slower than people of the same age because of breathlessness, or have to stop for breath when walking at my own pace.
3	I stop for breath after walking about 100 yards [91 meters] or after a few minutes on level ground
4	I am too breathless to leave the house or I am breathless when dressing

Figure 4. Modified Medical Research Council dyspnea scale; Adapted from: Fletcher CM, Elmes PC, Fairbairn AS, Wood CH. The significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population. Br Med J 1959; 2:257.

an exacerbation on dual bronchodilator therapy. Triple therapy is also reserved for those at higher risk of future exacerbations and mortality, as indicated by those who have experienced 2 or more moderate exacerbations in the previous year or 1 or more severe exacerbations. In this cohort with frequent exacerbations, single inhaler triple therapy has demonstrated evidence of significant exacerbation reduction compared to dual bronchodilator therapy, as well as data indicating an all-cause mortality reduction. De-escalation from single inhaler triple therapy is not recommended. Initial pharmacotherapy with less than triple therapy for this group of patients who frequently experience exacerbations is not recommended. These patients deserve inhaled therapy with demonstrated evidence to prevent the exacerbation events driving their high-risk phenotype.

Mild COPD Example:

43 years of age

Chief complaint: Shortness of breath when climbing stairs and occasional morning cough and sputum.

A 22 pack-year tobacco history, morning chronic bronchitis phenotype, absence of exacerbations, a modified MRC grade of 1 for dyspnea. Post-bronchodilator spirometry demonstrating mild COPD with an obstructed ratio of 0.64 and an FEV1 of 84%. **Recommended initial pharmacotherapy:** LAMA or LABA with a SABA reliever.

Moderate Spirometric COPD With Infrequent Exacerbations Yet a High Symptom Burden

52 years of age

Chief complaint: Shortness of breath when walking with spouse and with weekend activities such as grocery, shopping, and indoor chores.

A 27 pack-year tobacco history, morning chronic bronchitis phenotype, a modified MRC grade of 2 for dyspnea with a CAT score of 19, with 1 outpatient lower respiratory tract infection treated at a walk-in clinic with an antibiotic within the past 12 months. Post-bronchodilator spirometry demonstrating moderate COPD with an obstructed ratio of 0.57 and an FEV1 of 64%. **Recommended initial pharmacotherapy:** LAMA/LABA dual bronchodilator therapy with a SABA reliever.

Frequently Exacerbating COPD With a High Symptom Burden and Moderate Airway Obstruction

61 years of age

Chief complaint: Requested a primary care physician follow-up appointment to review the emergency department visit for a chest infection requiring an antibiotic and prednisone.

A 31 pack-year tobacco history, morning chronic bronchitis phenotype, a modified MRC grade of 2 for dyspnea with a CAT score of 15, with 1 exacerbation treated in the emergency department on an outpatient basis in the past 12 months with an antibiotic and prednisone. Post-bronchodilator spirometry demonstrating moderate COPD with an obstructed ratio of 0.59 and an FEV1 of 71%. **Recommended initial pharmacotherapy:** LAMA/LABA/ICS single inhaler triple therapy.

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