

Strategies for Preventing COPD Exacerbations

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LEARNING OBJECTIVES

After participating in this activity on chronic obstructive pulmonary disease (COPD), family physicians will be better able to:

- **Identify** symptomatic patients at increased risk of COPD to prompt early diagnostic evaluation
- **Individualize** evidence-based therapy with the goal of reducing COPD exacerbations and improving patient outcomes
- **Identify** the role of fixed triple-combination inhalers as part of individualized therapy

It's natural to think about the burden of chronic obstructive pulmonary disease (COPD) in terms of the prevalence (6% of US adults),^{1,2} mortality (fourth leading cause of death at a rate of 44 deaths per 100,000 US population),^{3,4} and total cost of care (\$49 billion/year).⁵ Although sobering, these statistics don't adequately capture the patient perspective, where the burden of COPD generally is characterized as daily symptoms, limited activity, poor quality of life, and contributing to fear of acute worsening of respiratory symptoms (previously called exacerbations), often leading to hospitalization and early death.^{6,7} In fact, COPD is a leading cause of

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CONFLICT OF INTEREST

Dr. Yawn discloses that she has served on advisory boards for GlaxoSmithKline, AstraZeneca, Novartis and Boehringer Ingelheim. She is a consultant for GlaxoSmithKline on epidemiology studies of COPD and herpes zoster and has an investigator initiated grant to study patient and clinician awareness of risk of HZ in people with COPD.

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disability, accounting for 1.2 million years lived with disability in the United States in 2016.⁸

A survey of patients with COPD who were hospitalized for acute worsening of respiratory symptoms identified 6 major unmet needs: (1) understanding of disease: most correctly identified their diagnosis and recognized their symptoms worsening over time, but only one-half understood their disease severity and prognosis; (2) symptoms: breathlessness was universal and severe; (3) physical limitations: COPD prevented participation in activities; (4) emotional distress: depressive symptoms and/or anxiety were present in most participants; (5) social isolation: most identified social limitations and felt confined to their homes; and (6) concerns about the future: one-half expressed fear about their future.⁹

To improve the health outcomes of these patients by reducing COPD-related hospital readmissions, the American Thoracic Society identified barriers to optimal care¹⁰:

- Poor communication
- Ineffective discharge guidance
- Lack of effective follow-up
- Limited efforts to engage patients and family
- Patient not being placed at the center of care
- Fragmentation of system/differences in where individual seeks care.

More recently, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) has provided several key recommendations¹¹:

1. The management strategy for stable COPD patients should be based on assessment of symptoms and risk of exacerbations.
2. The assessment should determine the level of airflow limitation, its impact on the patient's health status, and the risk of future events (eg, exacerbation, hospitalization, or death).
3. All individuals who smoke should be strongly encouraged and supported to quit.
4. The main treatment goals are reduction of symptoms and future risk of exacerbations.
5. The goal for treating COPD exacerbations is to minimize the negative impact of the current exacerbation and to prevent a future event.
6. Following an exacerbation, appropriate measures for preventing a future event should be initiated.

FIGURE 1. COPD assessment in primary care to identify undiagnosed respiratory disease and exacerbation risk questionnaire²¹

For each question, place an X in the box with the answer that is best for you. There are no right or wrong answers, only answers which are right for you.

Please answer each question	No	Yes	
1. Have you ever lived or worked in a place with dirty or polluted air, smoke, second-hand smoke, or dust?	<input type="checkbox"/>	<input type="checkbox"/>	
2. Does your breathing change with seasons, weather, or air quality?	<input type="checkbox"/>	<input type="checkbox"/>	
3. Does your breathing make it difficult to do things such as carry heavy loads, shovel dirt or snow, jog, play tennis, or swim?	<input type="checkbox"/>	<input type="checkbox"/>	
4. Compared to others your age, do you tire easily?	<input type="checkbox"/>	<input type="checkbox"/>	
	0	1	2 or more
5. In the past 12 months, how many times did you miss work, school, or other activities, due to a cold, bronchitis, or pneumonia?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

For questions 1-4, no = 0; yes = 1. Maximum total = 6.

Abbreviation: COPD, chronic obstructive pulmonary disease.

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SCREENING/CASE FINDING

A key objective identified by GOLD is early detection of COPD.¹¹ One approach is to identify persons at increased risk of COPD before signs and symptoms of the disease develop. This approach has been systematically investigated by the United States Preventive Services Task Force, which found a lack of evidence of benefit for screening on quality of life, morbidity, or mortality in asymptomatic patients.^{12,13}

Another approach for the early detection of COPD is to identify patients with symptoms and signs of COPD that the patient and family physician have not recognized.¹⁴ GOLD advocates case finding in this population.¹¹ Patients who fit into this population include smokers in their 30s who don't have asthma, but have had a lower respiratory tract infection treated with antibiotics or oral corticosteroids. Some patients with COPD attribute the slow decline in lung function and compensatory activity limitation as consequences of aging, obesity, poor conditioning, or smoker's cough.¹⁵ Such changes often become their new normal. Family physicians might not ask patients about chronic respiratory symptoms or fail to note the importance of recurrent respiratory events.^{15,16} The use of validated tools to identify chronic or recurrent respiratory symptoms in the primary care setting has demonstrated up to a 4-fold increase in COPD diagnoses, indicating under recognition of patients with symptomatic COPD.¹⁷⁻²⁰

The COPD Assessment in Primary Care to Identify Undiagnosed Respiratory Disease and Exacerbation Risk (CAPTURE) questionnaire was developed to identify patients with undiagnosed, yet symptomatic COPD who would benefit

from treatment with available therapies if the COPD diagnosis is confirmed.²¹ The 5-item self-administered questionnaire asks patients about symptoms, impact, and acute respiratory illness (FIGURE 1).²¹ Patients with a CAPTURE score of 0 or 1 are not considered at risk of an exacerbation or to have moderate-to-severe airflow obstruction (ie, forced expiratory volume over 1 second [FEV₁] <60% of predicted); therefore, further evaluation is not warranted. Patients with a CAPTURE score of 5 or 6 are considered to have a high likelihood of symptomatic respiratory disease and/or exacerbation risk and should undergo further evaluation, including spirometry. Patients with a CAPTURE score of 2, 3, or 4 should undergo peak expiratory flow testing. It is important to note that the CAPTURE questionnaire is not intended to identify patients with mild COPD (ie, FEV₁ >60% predicted and no exacerbation in the prior 12 months).

DIAGNOSIS

The most characteristic symptom of COPD is chronic, progressive dyspnea, while cough with sputum production is found in <30% of patients. These symptoms might vary from day to day and could occur before development of airflow limitation by many years. Chronic respiratory symptoms or an acute exacerbation are the common reasons patients seek medical care. The presence of one or more of these respiratory symptoms should prompt further evaluation to identify the underlying cause(s). Disorders to be considered in the differential diagnosis include asthma, heart failure, and bronchiectasis. Differentiating asthma from COPD

TABLE 1. Differentiating COPD vs asthma

Feature	COPD	Asthma
History of tobacco smoking or exposure to other types of smoke	Most	Possibly
Symptoms first occur before age 35	Rare	Often
Family history	Uncommon	Common
History of atopic disease	Uncommon	Common
Chronic productive sputum	Common	Uncommon
Breathlessness	Persistent, progressive	Variable
Nighttime awakening with breathlessness and/or wheeze	Uncommon	Common
Significant diurnal or day-to-day variability of symptoms	Uncommon	Common
Lung function between symptoms	Abnormal	Normal/near normal

Abbreviation: COPD, chronic obstructive pulmonary disease.

often is challenging (TABLE 1)^{11,22}; COPD and asthma often are comorbid.²³

The history and spirometry form the basis of the COPD diagnosis.¹¹ Key aspects of the history include exposure to risk factors (tobacco and other smoke, occupational dusts, vapors, fumes, gases, biomass fuels, and chemicals), personal history (eg, childhood respiratory infections, low birthweight, genetic factors, congenital/developmental abnormalities), family history of chronic respiratory disease, pattern of symptom development, history of acute respiratory events, comorbidities, and impact on activities of daily living and quality of life. It is important to consider that one-quarter of patients who develop COPD do not have a smoking history. Spirometry is essential for the diagnosis because it is more specific for COPD than peak expiratory flow measurement.¹¹ Patients with COPD typically show a decrease in both FEV₁ and forced vital capacity (FVC).¹¹ A post-bronchodilator FEV₁/FVC ratio <0.70 confirms the presence of airflow limitation.¹¹

To assess for the presence of symptoms, the COPD Assessment Test (CAT) is preferred over the Modified British Medical Research Council (mMRC) Questionnaire¹¹ because CAT assesses symptoms beyond breathlessness, such as chest tightness, sleeping soundly, and confidence to leave home.²⁴ A CAT score ≥10 (maximum 40) indicates the need to consider symptomatic treatment.^{11,25} A limitation of CAT is that it does not categorize patients into symptom severity groups for treatment purposes.

The CAT score has been combined with the FEV₁ and history of moderate or severe exacerbations to form the ABCD assessment tool which is used for the diagnosis, prognosis, and development of an individualized treatment plan. The refined ABCD assessment tool includes a number and letter (FIGURE 2).¹¹ The number relates to the GOLD grade of severity of airflow limitation, which is based on the FEV₁, while the letter relates to the symptom burden, which is based on the CAT (or mMRC) score and history of exacerbations. The

refined ABCD tool facilitates greater treatment individualization based on parameters that are driving the patient's symptoms at any given time.

PREVENTING FUTURE ACUTE EVENTS

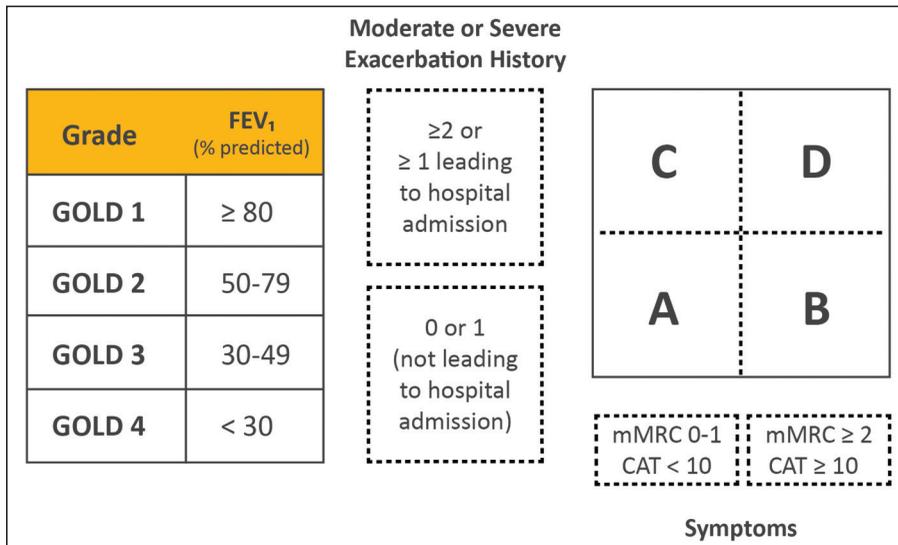
A key shift in treatment in recent years has been away from focusing on acute treatment of exacerbations to an emphasis on chronic treatment to maintain stable disease and prevent exacerbations and other events, such as hospitalization and death. This approach is analogous to the treat-to-target approach used for patients with type 2 diabetes mellitus.

In addition to eliminating or minimizing risk factors, this shift to preventive treatment requires early initiation of individualized, comprehensive therapy consisting of non-pharmacologic therapy, often including pulmonary rehabilitation, as well as combination pharmacologic therapy, with treatment escalation as needed based on symptoms and history of exacerbations. The importance of pulmonary rehabilitation should not be overlooked because of its benefits in improving symptoms, quality of life, and physical and emotional participation in everyday activities.¹¹ Holistic management directed at comorbidities and risk factors, as well as psychosocial support, is essential. As a chronic, debilitating, often fatal disease, it is important to provide team-based care that nurtures hope and supports patients to acquire knowledge, skills, and attitudes needed to self-manage their COPD.

INITIAL PHARMACOLOGIC TREATMENT

The choice of initial pharmacologic therapy in a patient with stable COPD is based on which 1 of the 4 ABCD groups the patient fits as determined by symptoms and exacerbation risk (FIGURE 3).¹¹ The choice within each class of medication depends on availability and the patient's responses and preferences. Patients in group A can be offered a short- or long-acting bronchodilator to reduce breathlessness, while patients in group B are best treated with a long-acting bron-

FIGURE 2. GOLD refined ABCD assessment tool¹¹

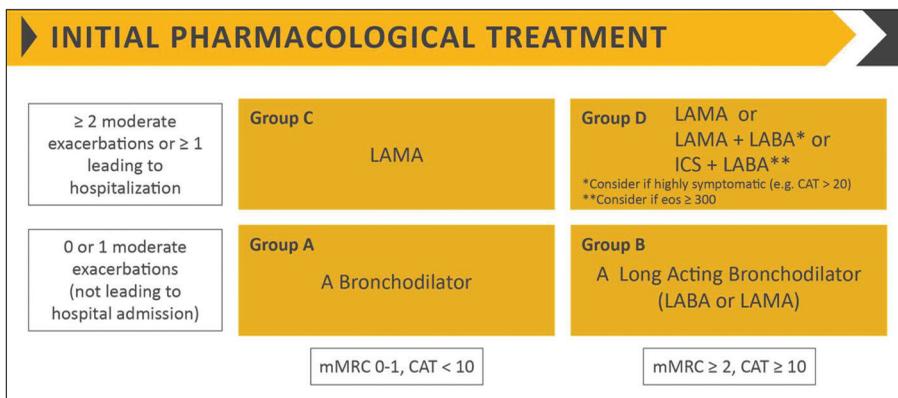


Example: Consider 2 patients – both patients with FEV₁ <30% of predicted, CAT scores of 18 and one with no exacerbations in the past year and the other with 3 moderate exacerbations in the past year. Both would have been labeled GOLD D in the prior classification scheme. However, with the new proposed scheme, the patient with 3 moderate exacerbations in the past year would be labeled GOLD grade 4, group D.

Abbreviations: CAT, COPD Assessment Test; FEV₁, forced expiratory volume in 1 second; mMRC, modified Medical Research Council dyspnea questionnaire.

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FIGURE 3. Initial pharmacological treatment¹¹



Abbreviations: CAT, COPD Assessment Test; COPD, chronic obstructive lung disease; eos, eosinophils; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; mMRC, modified Medical Research Council dyspnea questionnaire.

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chodilator, or, in the case of severe breathlessness, 2 bronchodilators. Treating patients in group C should consist of a single long-acting bronchodilator, preferably a long-acting muscarinic antagonist (LAMA).

A LAMA generally is appropriate as initial therapy for patients in group D. However, for patients with more severe

symptoms such as those with a CAT score ≥20, the combination of a LAMA plus a long-acting beta₂ agonist (LABA) is recommended. In patients with a history of asthma or blood eosinophil count ≥300 cells/μL, initial therapy with a LABA plus inhaled corticosteroid (ICS) is recommended. If breathlessness or exercise limitations persists or the patient develops exacerbations, escalation to inhaled triple therapy (ICS + LABA + LAMA) is recommended.¹¹

Inhaled medications

Localization of the COPD disease processes within the respiratory system lends itself to orally inhaled medication administration. Numerous orally inhaled medications for COPD are available, including nebulizers, pressurized metered-dose inhalers with/without spacers, soft-mist inhalers, breath-actuated metered-dose inhalers, and single- and multi-dose dry powder inhalers. Selection of an inhaler should be based on availability and storage requirements, as well as efficacy and safety.^{11,26} Patient factors include affordability, preference, and ability and understanding about proper use.^{11,26,27} For patients who require ≥2 inhaled controller medications, consider the same type of device for all inhaled medications prescribed for the patient.²⁸ Ideally, all inhaled controller medications should be available as dual or triple therapy in a single device. Advantages of combination inhalers is improved adherence and lower medication cost.²⁹

Two recent systematic reviews and meta-analyses assessed the safety and efficacy of single inhaler triple therapy with other inhaled medications for COPD, as well as separate inhalers of the 3 medications. The single inhaler triple therapies included ICS + LAMA + LABA. Two products are approved by the US Food and Drug Administration: fluticasone furoate/umeclidinium/vilanterol and budesonide/glyco-

TABLE 2. Checklist for the COPD follow-up office visit

<ul style="list-style-type: none"> • Repeat the CAT <ul style="list-style-type: none"> ○ Have patient complete in the waiting room or examination room^a
<ul style="list-style-type: none"> • Ask about: <ul style="list-style-type: none"> ○ Respiratory problems or events since last visit, particularly if they required an urgent care/emergency department visit ○ Changes in comorbidities ○ Changes in activity level (be specific) ○ Difficulties with prescription refills ○ Difficulties following the treatment plan ○ Satisfaction with treatment
<ul style="list-style-type: none"> • Observe inhaler technique <ul style="list-style-type: none"> ○ Can be done by trained staff
<ul style="list-style-type: none"> • Review medications the patient is taking to be sure they are the ones prescribed <ul style="list-style-type: none"> ○ Requires patient to bring in actual medications instead of a list ○ Brand might have been changed by pharmacist because of insurance
<ul style="list-style-type: none"> • Review patient's goals and action plan^a

Abbreviations: CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease.

^aCan be facilitated by using the COPD Foundation application (https://www.copdfoundation.org/Learn-More/The-COPD-Pocket-Consultant-Guide/Healthcare-Provider-Track.aspx?gclid=CjwKCAjwnlr1BRAWEiwA6GpwNZxd9C7JZuLRF55tEdWb-gVSLyVEc_YaNAi8puwJ_8nymlXeBVRlhoC31wQAvD_BwE)

pyrronium bromide/formoterol fumarate. A third product, beclomethasone dipropionate/glycopyrronium bromide/formoterol fumarate, is investigational. The recent approval of budesonide/glycopyrronium bromide/formoterol fumarate is based on the results of the phase 3 ETHOS trial. The ETHOS trial showed that at both the standard budesonide dose of 320 mcg and half-dose of 160 mcg demonstrated significant reductions in exacerbations compared with single inhaler dual therapy of glycopyrronium/formoterol fumarate and budesonide/formoterol fumarate, respectively, in patients with moderate to very severe COPD.³⁰ At the standard budesonide dose, the observed reductions in rate of moderate and severe exacerbations were 24% and 13% with the single inhaler triple therapy vs the single inhaler dual therapies, respectively. In addition, the single inhaler triple therapy showed a 46% reduction in the risk of all-cause mortality compared with glycopyrronium/formoterol fumarate.

The meta-analyses showed that the rate ratios for moderate-to-severe exacerbations with a single inhaler triple therapy were 0.69 (95% confidence interval [CI], 0.55 to 0.87) and 0.80 (95% CI, 0.71 to 0.90) vs LABA + LAMA and ICS + LABA dual therapy, respectively. Improvements in lung function and quality of life were greater with single inhaler triple therapy compared with single inhaler dual therapy (LABA + LAMA or ICS + LABA).^{31,32} Meta-analyses found no significant differences in several clinical endpoints, including exacerbations or FEV₁, between single inhaler triple therapy and triple therapy using 3 separate inhalers. In both analyses, the risk of pneumonia was significantly higher with single triple inhaler

therapy compared with LABA + LAMA (relative risk 1.38; 95% CI, 1.14 to 1.67³¹ and 1.53; 95% CI, 1.25 to 1.87³²) but not ICS + LABA dual therapy.

Individualizing inhaler selection and teaching and reinforcing proper administration technique have a direct impact on patient adherence and health outcomes.³³ Unfortunately, adherence often is poor and administration errors are common with inhaled medications; clinicians might not be familiar with proper administration technique.^{26,34-37} Moreover, clinicians do not routinely assess a patient's ability to use their prescribed inhaler.³⁸ Common errors in the use of an inhaler device relate to difficulties with inspiratory flow, inhalation duration, coordination, dose preparation, exhalation maneuver before inhalation, and breath-holding following dose inhalation.³⁹ In patients with a low peak inspiratory flow, for example, which is common after a severe exacerbation, it might be best to avoid using a higher resistance inhaler. When used properly, there appear to be no clinically important differences among the devices, including hand-held devices vs nebulized therapy.^{11,40}

FOLLOW-UP VISITS

The shift to preventing exacerbations and other acute events as a primary treatment goal makes frequent follow-up visits critical so that the treatment plan can be adjusted as needed based on patient symptoms, as well as difficulties he or she might be experiencing (TABLE 2).¹¹ The written treatment plan, which is indispensable to promote effective patient self-management,^{41,42} should be updated to reflect any changes. ●

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