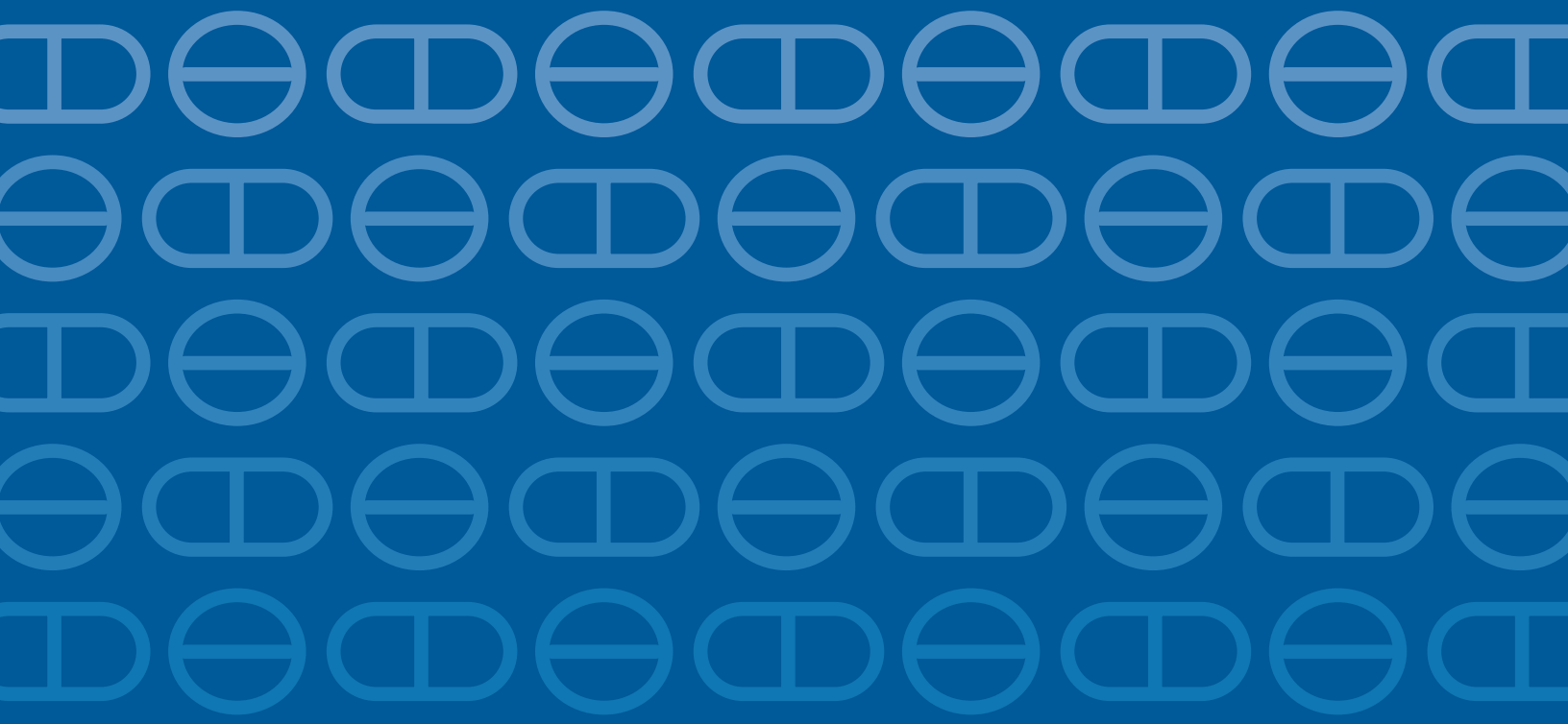
PACE Pharmaceutical Assistance Contract for the Elderly

Alosa Health
Balanced information for better care

Helping patients with COPD breathe easier

Managing chronic obstructive lung disease in primary care



Helping patients with COPD breathe easier:

Managing chronic obstructive lung disease in primary care

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These are general recommendations only; specific clinical decisions should be made by the treating clinician based on an individual patient's clinical condition.

Alosa Health

Helping patients with COPD breathe easier

Activity Start Date: June 18, 2025
Activity Termination Date: June 17, 2028

This activity offers CE credit for:

1. Medicine (AMA)
2. Nurses (ANCC)
3. Other

All other attendees will receive a Certificate of Attendance

Activity Overview:

The goal of the educational program is to help practitioners assess the comparative effectiveness and safety of medications used to manage the symptoms of COPD; understand the evidence regarding appropriate therapy; weigh the benefits, risks, and value of treatment options; and improve the quality of prescribing and patient care.

The educational program includes a written evidence report (print monograph) and several non-CME/CE components:

1. Summary document of top 4-5 key messages
2. “Academic detailing” educational sessions in clinicians’ offices with trained outreach educators (pharmacists, nurses, physicians) who present the material interactively
3. Reference cards for easy access to key materials
4. Patient education information (brochure/tear off sheets)

This program synthesizes current clinical information on this topic into accessible, non-commercial, evidence-based educational material, which is taught interactively to providers by specially trained clinical educators.

Learning Objectives:

After completing this activity, participants will be able to:

- Use spirometry data, clinical symptoms, and risk factors to identify and/or diagnose COPD.
- Select initial management strategies based on symptoms and history of exacerbations according to the latest GOLD guidelines.
- Describe when an inhaled corticosteroid may be indicated and when it should be discontinued.
- Among current smokers, assess smoking status and encourage cessation at each visit.
- Identify non-pharmacologic interventions, such as exercise regimens, good nutrition, and immunizations for all patients with COPD.
- Instruct patients on proper use of inhalers and nebulizers.

- Prescribe or recommend additional therapies as COPD severity worsens, such as azithromycin, roflumilast, dupilumab, ensifentrine, and oxygen therapy.
- Describe treatment of acute exacerbations with short-acting bronchodilators, systemic steroids, and antibiotics where appropriate.

Financial Support:

There is no commercial support associated with this activity.

Target Audience:

The educational program is designed for physicians, including general internal medicine doctors, family practice physicians, nurse practitioners, physician assistants, nurses, and all other clinicians caring for patients who have COPD.

Credit Information:

In support of improving patient care, this activity has been planned and implemented by CME Outfitters, LLC and Alosa Health. CME Outfitters, LLC is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

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Note to Osteopathic Physicians: The AOA automatically recognizes *AMA PRA Category 1 Credit* ™ as AOA Category 2 credit.

Note to Nurse Practitioners: Nurse practitioners can apply for *AMA PRA Category 1 Credit™* through the American Academy of Nurse Practitioners (AANP). AANP will accept *AMA PRA Category 1 Credit™* from Jointly Accredited Organizations. Nurse practitioners can also apply for credit through their state boards. The content of this CNE activity pertains to Pharmacology.

Nurses: This activity is designated for 1.5 nursing contact hours.

California Residents: This continuing nursing education activity was approved by the California Board of Registered Nursing. CME Outfitters LLC's provider number is CEP15510.

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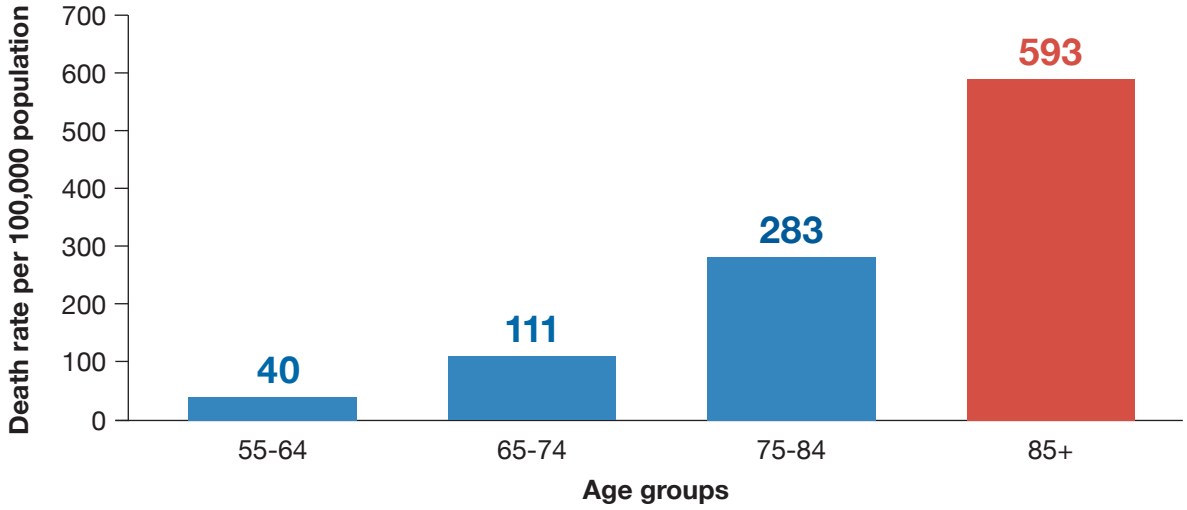
Table of Contents

The burden of COPD

Chronic obstructive pulmonary disease (COPD) is a significant national and global public health problem. It is the sixth-leading cause of death in the U.S., accounting for 147,382 deaths in 2022.[1] Older adults bear the highest burden of COPD-related mortality (Figure 1).[2] Nearly 16 million Americans have been diagnosed with COPD, although the actual prevalence may be higher because many cases are undiagnosed until symptoms become severe.[3] COPD prevalence varies substantially by income level, with prevalence in the poorest quintile nearly four times higher (16.3% in 2018) than in the wealthiest quintile (4.4%).[4]

This report summarizes the current understanding of COPD and presents evidence-based clinical guidelines for its diagnosis and treatment in primary care.

Figure 1: COPD-related mortality by age[2]



Pathophysiology

COPD, as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD), is a spirometric diagnosis of persistent, irreversible airflow limitation associated with exposure to noxious environmental stimuli (e.g., smoking, indoor fires, pollutants)[5] and respiratory symptoms such as dyspnea on exertion, wheeze, cough, and/or sputum production.[6]

Previous definitions of COPD emphasized chronic bronchitis and emphysema. Current definitions do not focus on these categories, because they often exist together and treatment approaches are based on clinical disease activity. Chronic bronchitis is marked by daily cough and sputum production for at least three months in each of two consecutive years; however, it is not necessarily associated with airflow limitation. Emphysema is a radiographic or histologic diagnosis, characterized by destruction of the alveoli and lung tissue, with subsequent loss of pulmonary elasticity.[7] Emphysema contributes to airflow obstruction, is an important phenotype for treatment and prognosis of COPD, and is also often apparent

on CT scan. However, emphysema can be identified on CT in the absence of airflow obstruction, and vice versa. In fact, in pathologic studies, narrowing and disappearance of small airways appears to precede the development of emphysema and acts as the major contributor to obstruction.[7]

Asthma is characterized by variable and recurring symptoms, with reversible airflow obstruction caused by bronchospasm and mucosal inflammation. COPD results from pathological changes in the central airways, peripheral airways, lung parenchyma, and pulmonary vasculature. Asthma tends to be more T-helper 2 cell-mediated and eosinophilic, whereas COPD is more neutrophilic and macrophage-mediated. There are also overlapping cellular mechanisms, and some patients may have asthma-COPD overlap syndrome.

Macrophages, neutrophils, and T- and B-lymphocytes release inflammatory mediators that interact with cells in these sites. In addition to inflammation, a protease/anti-protease imbalance exists in the lungs of patients with COPD, which leads to parenchymal destruction and increased mucus secretion. Oxidative stress further contributes to COPD pathophysiology by damaging or killing cells.

These pathogenic mechanisms may result in:

- chronic airway inflammation
- mucous gland hypertrophy and goblet-cell hyperplasia, with increased mucus secretion
- narrowing of smaller airways and fibrosis
- airflow obstruction and a decrease of elastic recoil, making complete exhalation difficult
- trapping of air in the lungs, resulting in hyperinflation and reduced inspiratory capacity, accentuated during exercise (“dynamic hyperinflation”), which is a major cause of dyspnea in patients with severe disease
- destruction of alveoli, impairing gas exchange and leading to hypoxemia and hypercapnia
- hypoxic vasoconstriction of pulmonary arterioles, causing pulmonary hypertension[8]

The airflow limitation in COPD can often be partially ameliorated by bronchodilators, and some patients with chronic asthma develop irreversible airway narrowing. Because of this, it may not be possible to completely differentiate between patients with asthma whose airflow obstruction does not remit completely and patients with COPD who have partially reversible airflow obstruction.

Natural history

The course of COPD can be highly variable due to the complex interactions of genes with environmental exposures and individual risk factors. A substantial fraction of patients who develop COPD are likely at risk early in life from reduced lung growth or early decline in lung function.[9,10] Among patients with COPD, some have relatively stable lung function, and others have more rapid decline over time.[11] Exacerbations generally lead to lung function deterioration,[12] increased morbidity, more frequent hospitalizations, and reduced quality of life.[6,13] Progressive airflow limitation may lead to disability and early death.

Risk factors for developing COPD

Factors contributing to the development of COPD include:[5,14]

- smoking
- exposure to biomass (e.g., wood, dung, straw) smoke from fires for cooking or heating[15]
- occupational dust and fume exposure

- outdoor air pollution[16]
- genetic factors, most notably alpha-1 antitrypsin deficiency
- recurrent severe respiratory infections in childhood
- maternal smoking during pregnancy
- asthma

Smoking is by far the most common contributing cause to COPD in industrialized countries, although exposure to biomass smoke is a substantial global risk factor.[17] At a population level, the amount of tobacco smoked is closely related to the rate of decline in FEV_1 (Forced Expiratory Volume in 1 second), although individuals vary greatly in their susceptibility to lung damage from tobacco smoke.

It is commonly believed that only 15-20% of smokers develop COPD, however this may be an underestimate because many smokers with mild to moderate symptoms are not diagnosed with COPD even though they would likely meet the diagnostic criteria by spirometry.[18] In susceptible smokers, cigarette smoking results in a steady decline in lung function, with a decrease in FEV_1 of 25-100 mL/year.[19] About 20% of COPD among U.S. never-smokers is attributable to occupational dust and fumes.[20] Urban/outdoor air pollution likely only accounts for a small percentage of COPD prevalence, although it may be a significant trigger for exacerbations.[16]

Comorbid conditions

Patients with COPD, particularly those with advanced disease, frequently have significant comorbidities.[5] An analysis of comorbidities in 291,978 COPD patients in a nationally representative Medicaid claims data set found that acute care, hospital bed days, and total Medicaid-reimbursed costs increased as the number of comorbidities increased.[21] The most prevalent comorbidities were hypertension (46%), diabetes (31%), psychiatric disorders such as anxiety and depression (27%), hyperlipidemia (20%), and asthma (18%).[21]

BOTTOM LINE: COPD is a common disease that is largely preventable. Think about COPD for any patient with dyspnea, wheeze, chronic cough, chronic sputum production, and exposure to inhaled toxins, particularly tobacco smoke.

Identification and diagnosis

COPD is substantially under-recognized, perhaps in part because the availability of spirometry, which is necessary for a diagnosis, may be limited in resource-poor areas. Symptoms that can precede COPD, such as mucus hypersecretion, often occur in people younger than age 50.[22] Early identification or diagnosis is important for prompt treatment that can slow progression of the disease, improve pulmonary function, relieve symptoms, reduce the frequency of exacerbations, improve quality of life, and reduce morbidity and mortality.[5,23]

Medical history

When assessing a patient for COPD, the medical history should include:[5,24]

- Frequency and intensity of pulmonary symptoms including cough, dyspnea, sputum production/purulence, wheezing, and chest tightness or pain
- Exposure to tobacco smoke, occupational dusts and chemicals, smoke from home cooking and/or heating
- Past medical history, including asthma, allergies, sinusitis, or nasal polyps; respiratory infections in childhood; other respiratory diseases
- Functional capacity and impact of symptoms on quality of life, including limitations of activity, missed work and economic impact, and effect on family
- Family history of COPD, other chronic respiratory diseases, or lung cancer
- History of exacerbations or previous hospitalizations for respiratory disorders. Patients not yet diagnosed may not recognize these as COPD exacerbations but the episodes can be identified based on prescriptions for antibiotics and/or systemic steroids for a respiratory illness.
- Presence of comorbidities such as heart disease, osteoporosis, musculoskeletal disorders, gastroesophageal reflux disease, depression, anxiety, or malignancies
- History of unexplained weight loss

Patients with more advanced disease may not report dyspnea because they adapt to their condition by restricting activities that causes breathlessness, or have concurrent cardiac or musculoskeletal conditions that limit their ability to exercise. Assessment of exercise tolerance can allow for earlier detection of COPD in some patients.[25]

Physical examination

The physical examination is often normal in early COPD. No single finding or combination of findings rules out airflow limitation. Signs suggesting airflow limitation include wheezing, barrel chest, hyper-resonance, and use of accessory muscles of respiration. Polyphonic wheeze suggests diffuse bronchospasm, and rhonchi suggest focal bronchial narrowing from mucus.[26]

Examination may also reveal evidence of complications from COPD such as heart failure with preserved ejection fraction (e.g., peripheral edema or elevated jugular venous pressure) in patients with more advanced disease.

Pulse oximetry

Measure oxygen saturation with pulse oximetry in all patients presenting with dyspnea or suspected of having COPD. If peripheral saturation is <92%, arterial blood gases should be assessed and supplemental oxygen considered (see more detail in the section on supplemental oxygen on page 31).[5]

Spirometry

Spirometry is required for the diagnosis of COPD and provides prognostic information. It is the most reproducible, standardized, and objective way of measuring airflow limitation. Spirometry can be performed in the office by physicians, nurses, or other healthcare team members trained in the procedure, or it can be done in a pulmonary function testing laboratory (available in many hospitals or medical facilities).

Because early COPD may be minimally symptomatic, spirometry can help detect early disease.[27] Conversely, many current and former smokers have respiratory symptoms but do not have COPD.[28] Spirometry should also be performed whenever a significant worsening of symptoms or a major complication occurs. Spirometry in stable disease can provide useful information on the rate of decline in lung function and is recommended at least annually.[5]

The functional value measured by spirometry is the ratio between:

- **FEV_1:** the volume of air exhaled during the first second of a forced expiration starting from maximal inspiration.
- **Forced Vital Capacity (FVC):** the maximum volume of air that the patient can forcibly exhale after taking the deepest breath possible.

Spirometry should be performed before and after the administration of bronchodilators when assessing patients with suspected COPD. A post-bronchodilator $FEV_1/FVC < 0.7$ in the appropriate clinical setting confirms the diagnosis of COPD.[5] Patients with an $FEV_1/FVC < 0.7$ before bronchodilator administration and ≥0.7 after bronchodilator administration do not meet criteria for COPD. Such patients, along with those whose FEV_1 improves substantially after bronchodilators (at least 10% increase in either FEV_1% predicted or FVC% predicted)[29], are more likely to have asthma.[30] Distinguishing between COPD and asthma is important, as the treatment strategies for the two diseases differ, although they can co-exist or have overlapping pathophysiology.

The FEV_1/FVC ratio declines with age in normal patients, and thus this metric has been criticized for potentially under-diagnosing younger patients and over-diagnosing older patients. However, GOLD advocates the use of this absolute ratio due to the simplicity of interpretation, the independence of the measure from reference values, and because this criterion was used in all the clinical trials that form the evidence base for treatment recommendations. The GOLD grades of obstruction (all with $FEV_1/FVC < 0.7$) are as follows:[5]

- Mild; $FEV_1 \geq 80\%$ predicted
- Moderate; $50\% \leq FEV_1 < 80\%$ predicted
- Severe; $30\% \leq FEV_1 < 50\%$ predicted
- Very Severe; $FEV_1 < 30\%$ predicted

Note that, although the administration and interpretation of pulmonary function tests are largely the purview of pulmonologists, primary care physicians should be aware that in 2021 the European Respiratory Society and the American Thoracic Society officially discouraged the use of race adjustments in pulmonary function test interpretation because they can lead to misdiagnosis.[31] In 2022, race-based equations were changed to race-neutral equations. Weighted averages across racial groups should be used instead of individual by-group averages. Adjustments for age, sex, and height continue to be used in the context of pulmonary function testing.

The spirometric grade predicts population-level outcomes and is used in decisions for some non-pharmacologic therapies (such as lung volume reduction and transplant) although it does not correlate with individual outcomes or exacerbations and, therefore, is no longer part of clinical severity staging. Figure 2 presents the airflow limitation observed in patients with COPD.

Figure 2: Volume-time curve of a patient with COPD[32]

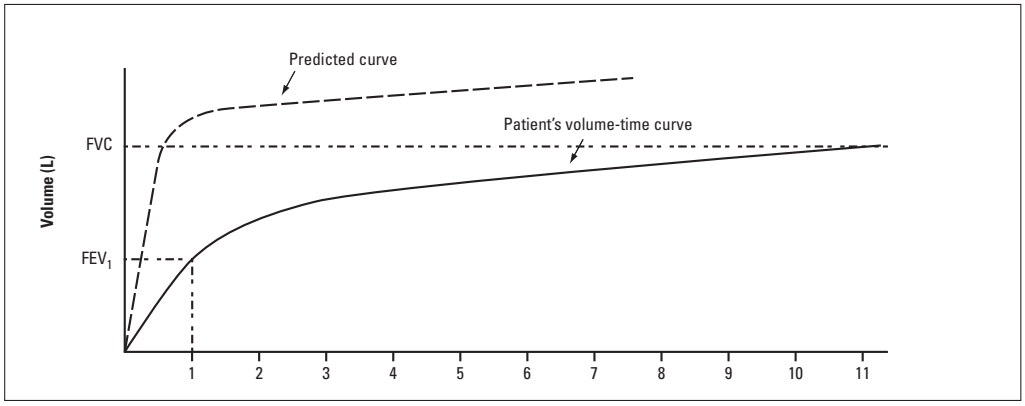


Figure 2. Volume-time curve of a patient with COPD. Airway obstruction is indicated by the significant straightening of the patient's curve compared with the predicted curve.

FEV_1: forced expiratory volume in 1 second FVC: forced vital capacity

Reprinted with permission from *BC Medical Journal*. 2008;50(2):98. X-axis is respiratory time in seconds.

The U.S. Preventive Services Task Force does not recommend screening spirometry in asymptomatic patients, regardless of smoking status, because a systematic review of the evidence found that early detection of COPD did not change the time course of the disease or patient outcomes.[33] That said, some studies suggest that early detection of COPD in asymptomatic high-risk patients (e.g., heavy smokers or those with recurrent chest infections) could lead to improved outcomes.[5,34]

COPD staging: The GOLD groups

The 2025 GOLD criteria use airflow obstruction as measured by spirometry only for diagnosis, prognosis estimates, and guidance of certain non-pharmacologic treatments. Symptoms and frequency of exacerbations should guide initial pharmacologic treatment decisions.[5]

Symptoms

Symptoms including dyspnea, cough, sputum, and the frequency of exacerbations can help guide treatment and inform prognosis. Several easy-to-use tools are available for assessing these symptoms. One is the COPD Assessment Test (CAT), a short patient-completed questionnaire with reliable measures of cough, phlegm, chest tightness, breathlessness going up hills/stairs, activity limitation at home, confidence leaving home, sleep, and energy.[35] CAT is available in many languages.

A similar, but even shorter, tool is the modified Medical Research Council (mMRC) dyspnea scale (Table 1).[5,36]

Table 1: mMRC dyspnea scale

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 or after a few minutes on level ground
4	I am too breathless to leave the house or I am breathless when dressing

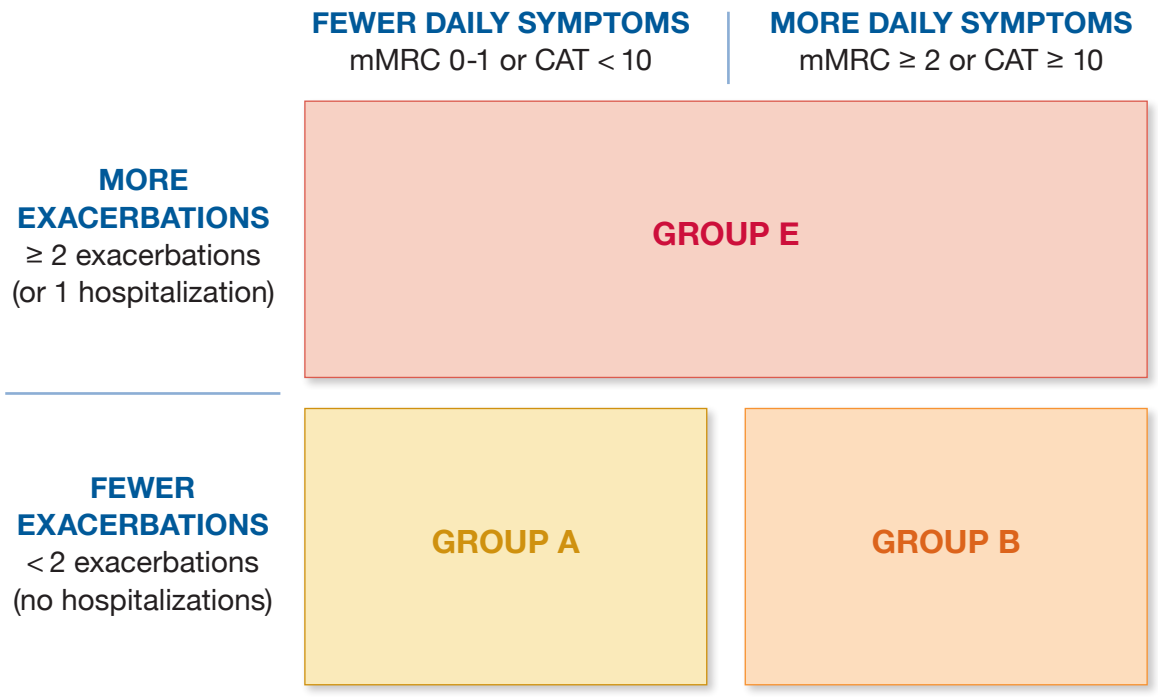
The 2025 GOLD guidelines use either the mMRC or CAT score for assessing symptom burden.

Exacerbations

As defined by the GOLD guidelines, a COPD exacerbation is an event characterized by dyspnea and/or cough and sputum that worsen over the course of 14 days or less.[5] Since these symptoms are not specific to COPD, and since exacerbations exist on a continuum of mild to severe, relevant differential diagnoses should be considered, see page 27.

The GOLD classification system for patients with COPD is based on the number of exacerbations in the previous year and daily symptom severity (Figure 3). Patients with fewer exacerbations are divided into either Group A (with fewer symptoms) or Group B (with more symptoms). Patients with relatively more exacerbations are placed in Group E, regardless of the number of symptoms. Pharmacologic options appropriate for each category will be discussed in the following section.

Figure 3: The 2025 GOLD classification system[5,*]



* Exacerbations refers to COPD related exacerbations and hospitalization for COPD.

Additional assessment tools

Chest imaging

A chest X-ray is not diagnostic for COPD but can be useful in identifying or excluding other conditions such as pneumonia, heart failure, lung cancer, pleural effusions, tuberculosis, and pneumothorax.[37] Similar considerations apply to chest CT scans, which may show emphysema and flattened diaphragms, but are not diagnostic for COPD. Moreover, many patients with COPD may meet criteria for CT scans to screen for lung cancer due to smoking history.

Alpha-1 antitrypsin deficiency

Alpha-1 antitrypsin deficiency (AATD) may cause respiratory symptoms in patients who develop COPD at a young age (typically <45 years), who have a strong family history of the disease, or who have unexplained liver disease. Testing may also be helpful in symptomatic patients under the age of 55 who do not have a substantial history of tobacco smoke or other environmental risk exposure. Testing should include measurement of the serum alpha-1 antitrypsin level, followed by genotyping or protein phenotyping if the level is low.[38,39] In addition to testing high-risk patients (as defined above), some organizations, including the World Health Organization, have recommended testing for AATD in all patients diagnosed with COPD.[24,40]

BOTTOM LINE: Use spirometry to diagnose COPD and use symptoms and history of exacerbations to classify patients according to GOLD groups, which will guide initial pharmacologic treatment decisions.

Managing stable COPD

Goals and principles of management

Appropriate treatment can alter the natural history of the disease, and non-pharmacologic approaches may be particularly beneficial.[41] The goals of COPD management are to relieve symptoms, reduce exacerbations, prevent lung function decline, and improve quality of life.[5]

All patients with COPD benefit from the following interventions:[5]

- for those who smoke, efforts to cut back or quit using pharmacologic and/or behavioral therapy
- exercise
- adequate nutrition
- self-management education, including proper inhaler use
- immunization against agents causing lung diseases

Some patients with COPD also benefit from the following:

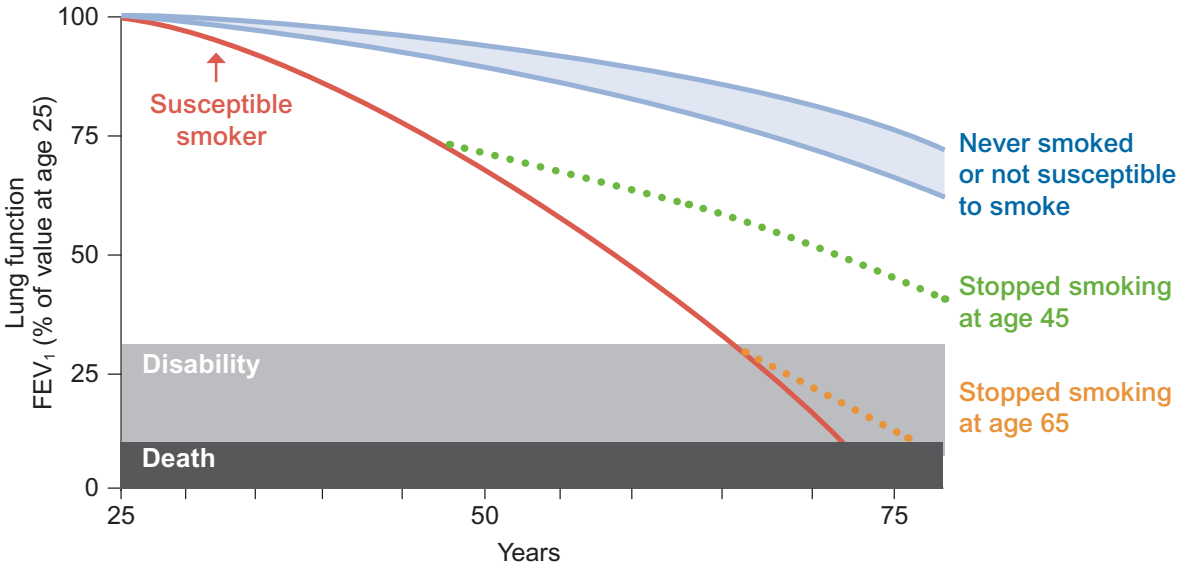
- pulmonary rehabilitation
- medications (inhalers, nebulizers, pills, injections)
- supplemental oxygen
- palliative care

Smoking cessation

Smoking cessation is the single most effective intervention to delay the development of COPD, slow the rate of decline in lung function once COPD is present, and delay the onset of disability and subsequent mortality.[19,42] The rate of smoking in Pennsylvania (15%) is higher than the national average (12%).[43] A 2008 systematic review found that smoking cessation slows the rate of lung function decline and improves survival, even in patients with severe COPD.[44] Smoking cessation also reduces the risk of exacerbations, with the magnitude of the reduction dependent upon the duration of abstinence.[45] Unfortunately, many patients are not encouraged to quit smoking when they see a clinician. According to a 2020 report by the U.S. Surgeon General, 66% of patients were screened for tobacco use during outpatient visits and only 20% of those who said they were current tobacco users reported receiving any counseling or education about smoking cessation during a visit.[46]

Figure 4 shows the rate of loss in FEV_1 for a non-smoker compared to a susceptible smoker, the onset of symptoms and disability, and the potential effect of stopping smoking early or late in the course of COPD. The curves represent the mean of many individual smokers, who have different rates of loss, with onset of symptoms and disability at different ages. Note that symptoms may not produce disability until lung function has been significantly impaired. Many clinicians find this figure to be a powerful tool in educating patients about the importance of smoking cessation.

Figure 4: Smoking and decline of lung function in COPD[10,19]



Assessing the willingness to quit

Even a brief intervention by a clinician may help motivate a patient to quit smoking. The key steps for brief intervention are the "5 A's":[47]

- *Ask:* identify tobacco use at every visit; electronic systems that prompt clinicians to ask about smoking for every patient at every clinic visit may be helpful
- *Advise:* strongly urge all tobacco users to quit, using a clear, strong, and personalized message
- *Assess:* determine the patient's willingness to make a quit attempt
- *Assist:* help the patient with a quit plan, provide practical counseling, help the patient obtain social support, recommend use of medications as appropriate, and provide supplementary materials
- *Arrange:* schedule follow-up contact, either in person or by telephone

Counseling strategies for smoking cessation

For patients ready to make a clear commitment to quitting, the plan to assist them should contain both behavioral interventions and recommendations regarding pharmacologic therapy, since a comprehensive approach is more successful than any one mode of therapy.[48,49] A successful tobacco cessation program might include the following:[50]

- Social support: identify family/friends to enable the plan; identify social barriers that may hinder success (e.g., a smoking spouse); facilitate joining a smoking cessation support group if available
- Problem solving techniques: advise patients to anticipate smoking triggers, such as settings that often involve smoking; develop ways for dealing with anxiety and/or weight gain while quitting, such as an exercise program
- Screen for mental illness or substance use disorders since smoking prevalence is higher in these groups than the general population[51] and smoking cessation may be unsuccessful without treating these problems
- Recommendations for pharmacologic treatment: see below
- Set a quit date: preferably within 2 weeks of the provider encounter

Links to patient resources for smoking cessation may be found at smokefree.gov and at cdc.gov/tobacco/campaign/tips/quit-smoking/.

Providing brief advice that attempting to quit smoking increases the likelihood that someone who smokes will successfully quit and remain a nonsmoker 12 months later.[52] More intensive advice may result in slightly higher rates of quitting.[52] A Cochrane review found that high-intensity or low-intensity behavioral treatment increased abstinence rates versus usual care in smokers with COPD (risk ratios for quitting for high- and low-intensity, 25.4 and 2.18, respectively).[49]

Focused counseling sessions can have substantial effects, and can increase tobacco cessation success by up to 20%.[50] While there are no clear counseling components critical to a successful program, the number of sessions is important, with the greatest impact seen with four sessions of at least 10 minutes in length.[50] Phone follow-up by a non-MD provider is very useful.[53]

Medications to help with quitting

The pharmacotherapies presented in Table 2 can effectively support smoking cessation, unless contraindications are present:[54]

Table 2: Pharmacotherapies for smoking cessation

	Bupropion Wellbutrin, Zyban, generics	**Varenicline** Chantix	**Nicotine replacement therapy**
How provided	prescription only	prescription only	over-the-counter as gum, patch, lozenge, nasal spray
When to start	at least 1 week prior to quit date	at least 1 week prior to quit date ***or*** if patients are thinking of quitting in the near future	When cutting back or stopping tobacco product
Most common side effects	insomnia, agitation, dry mouth, headache	nausea, insomnia, vivid dreams, headache	irritation at delivery site
Notes	contraindicated in patients with seizure disorder	can be used in patients with psychiatric disorders[55]	can be used alone or in combination with prescription options

Varenicline (Chantix) was found to be superior to bupropion (Zyban, Wellbutrin, others) and a nicotine patch in **EAGLES**, the largest randomized trial to date comparing pharmacologic therapies for smoking cessation.[55] Other studies suggest that varenicline, bupropion, and nicotine replacement each have success rates of ~15-25%.[56-58] Nicotine replacement therapy (short- and long-acting) may be combined with either varenicline or bupropion to increase success rates. Choose therapy based on patient preference, cost, and the presence of any mitigating medical or psychiatric conditions.

Some points to consider for each therapy:

- Nicotine replacement therapy[59,60]
  - The aim is to treat symptoms of nicotine withdrawal: anxiety, irritability, insomnia, increased appetite and weight gain, decreased concentration, and depressed mood.
  - Cessation rates are higher with long-acting nicotine release formulations (transdermal patches) used in combination with a quick release product (gum, lozenge, inhaler, nasal spray) for acute nicotine cravings.
  - Use after myocardial infarction does not appear to increase cardiovascular events.
  - Incorrect use of nicotine lozenges and gum is common. Patients should "park" lozenges or gum near their cheeks to promote absorption.
- Varenicline[61]
  - To allow time for varenicline to take effect, a quit date should be set at least 1 week after starting the drug.
  - Most evidence suggests minimal or no increased risk of cardiovascular complications in patients with stable cardiovascular disease.[62] Though patients with acute coronary syndrome (ACS) in the 2 months before enrollment were excluded from EAGLES, other data show varenicline to be safe and effective after ACS.[63,64]
- Bupropion[65-67]
  - To allow time for bupropion to take effect, a quit date should be set at least 1 week after starting the drug.
  - This drug is theoretically beneficial in patients with co-morbid depression or schizophrenia, but may exacerbate mania symptoms in patients with bipolar disorder.
  - Avoid in patients at increased risk of seizures, as bupropion lowers the seizure threshold.
  - Evidence suggests this drug is safe but not effective in patients discharged after ACS.[68]
- Combination therapy
  - Nicotine replacement in conjunction with varenicline is superior to varenicline alone.[69,70]
  - Similarly, nicotine replacement in conjunction with bupropion may be more effective than bupropion alone, though this finding was not statistically significant in a large systematic review.[71]

The role of e-cigarettes

Electronic cigarettes (e-cigarettes) work by heating a liquid that usually contains nicotine and flavorings, which creates a vapor rather than smoke, thus sparing users from exposure to known harmful compounds in conventional cigarettes.[72] Some people use e-cigarettes to help them stop smoking tobacco. A 2025 study in England found that e-cigarettes were the most commonly-used smoking cessation aid, and were associated with a nearly two-fold increase in the rate of successful smoking cessation.[73] A Cochrane meta-analysis found that those using nicotine e-cigarettes were more likely to stop smoking for at least 6 months compared to nicotine replacement therapies (RR 1.59; 95% CI: 1.30-1.93 across 7 studies with 2544 participants) or e-cigarettes without nicotine (RR 1.46; 95% CI: 1.09-1.96 in six studies with 1613 participants).[72,74] A 2024 trial randomized 1246 participants to either an intervention group that received free nicotine e-cigarettes, standard smoking cessation counseling and optional nicotine replacement therapy, or to a control group that received standard counseling and a voucher for nicotine replacement therapy. At 6-month follow-up, 28.9% of patients in the intervention group had quit smoking (biochemically validated) vs. 16.3% in the control group (RR 1.77, 95% CI 1.43-2.20).[75]

Long-term studies of the potential health impacts of e-cigarettes have not been conducted. Adverse events reported in clinical trials with relatively short durations (e.g., <6 months) include throat/mouth

irritation, headache, cough, and nausea, all of which tended to dissipate with continued e-cigarette use.[72] Patients interested in using e-cigarettes as a smoking cessation aid should choose from those that have been authorized by the U.S. Food and Drug Administration (list available at qrco.de/FDA_ecigs). Note that FDA authorization does not mean the products have been deemed safe or "approved" by the FDA.

BOTTOM LINE: Smoking cessation is central in COPD management at all stages of the disease. It can slow the deterioration of lung function and reduce mortality. Support the patient with stopping or cutting back smoking with behavioral and pharmacologic options based on patient preference.

Pharmacologic therapy for stable COPD

Bronchodilators

Bronchodilators are the cornerstone of COPD pharmacotherapy. While they have not been shown to improve survival, they can significantly improve symptoms, lung function, and exercise performance, and can reduce the frequency of exacerbations.[5,76] Bronchodilators reduce airflow obstruction and hyperinflation, thereby relieving dyspnea, increasing inspiratory capacity, and decreasing the work of breathing, even with minimal improvement in spirometry findings.

The two major classes of bronchodilators are ß-agonists and muscarinic antagonists (also called anticholinergics), which can be used individually or in combination. The mechanisms of action of the two classes differ. The principal action of ß-agonists is to relax airway smooth muscle by stimulating $ß_2$-adrenergic receptors.[5] The most important effect of muscarinic antagonists in patients with COPD appears to be blockade of acetylcholine's effect on muscarinic receptors, resulting in smooth muscle relaxation.[5]

Short-acting inhaled bronchodilators

Short-acting ß-agonists (SABAs) and short-acting muscarinic antagonists (SAMAs) are the two types of short-acting bronchodilators. SABAs include albuterol (ProAir HFA, Proventil HFA, Ventolin HFA, and their generic and authorized generic formulations) and levalbuterol (Xopenex HFA and its authorized generic), while SAMAs include ipratropium (Atrovent HFA). Both may be used intermittently to relieve worsening symptoms such as dyspnea. The use of short-acting bronchodilators before an exercise session may reduce dynamic hyperinflation and improve exercise capacity. Most studies suggest that SABAs and SAMAs are equally effective in patients with COPD.[77] The choice between these agents depends on individual response and adverse effects.[5]

If an appropriate dose of a single agent does not adequately control symptoms, consider combining a SABA with a SAMA.[5] For example, albuterol in combination with ipratropium is available in a single soft mist inhaler (Combivent Respimat). The **COMBIVENT** trial found that this combination provided better bronchodilation in patients with COPD than either agent alone, without increasing adverse effects.[78]

Long-acting inhaled bronchodilators

Long-acting inhaled bronchodilators for COPD include long-acting ß-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs).

- **LABAs**: formoterol (Foradil Aerolizer, Perforomist), olodaterol (Striverdi), and salmeterol (Serevent).
- **LAMAs**: aclidinium (Tudorza), glycopyrrolate (Lonhala Magnair), revefenacin (Yupelri), tiotropium (Spiriva), and umeclidinium (Incruse).

A short-acting agent should be continued on an as-needed basis after initiation of a long-acting agent.

Inhaled corticosteroids

In vitro evidence suggests that inflammation in COPD has limited responsiveness to corticosteroids.[5] Most studies of inhaled corticosteroid (ICS) monotherapy show no benefits in terms of either FEV_1 or mortality.[79] However, inhaled steroids still have a role in the management of COPD when used in combination with long-acting ß-agonists and/or long-acting muscarinic antagonists.

Combination maintenance inhalers

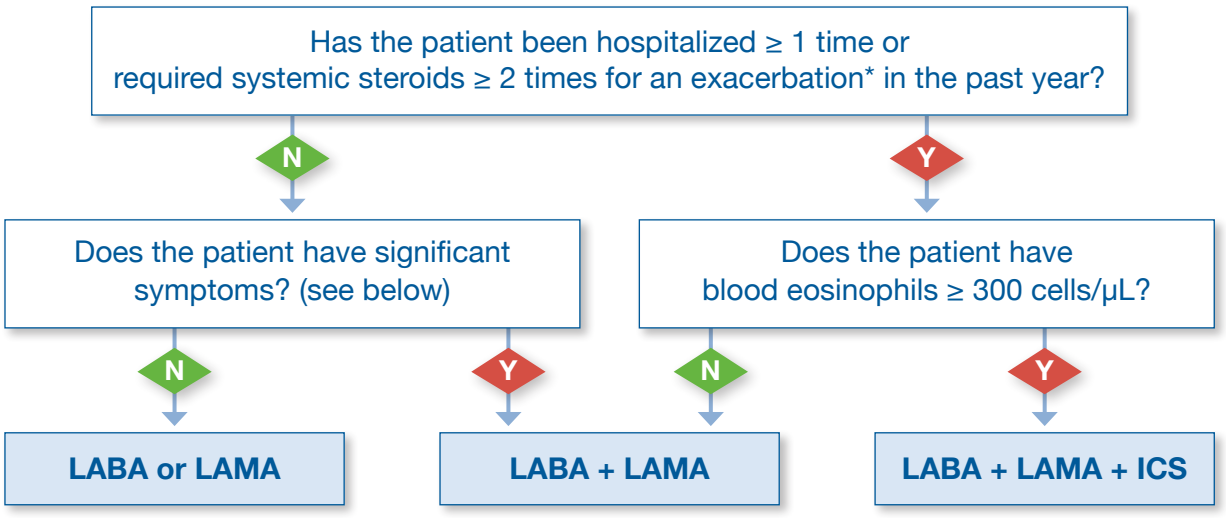
There are currently three categories of maintenance inhalers that combine the LABAs, LAMAs, and/or ICS discussed above:

- **LAMA + LABA:** aclidinium/formoterol (Duaklir); glycopyrrolate/formoterol (Bevespi Aerosphere); tiotropium/olodaterol (Stiolto Respimat); umeclidinium/vilanterol (Anoro Ellipta)
- **ICS + LABA:** budesonide/formoterol (Symbicort); mometasone/formoterol (Dulera); fluticasone/salmeterol (Advair, Wixela, AirDuo); fluticasone/vilanterol (Breo)
- **ICS + LAMA + LABA:** fluticasone/umeclidinium/vilanterol (Trelegy); budesonide/glycopyrrolate/formoterol (Breztri Aerosphere)

GOLD guidelines for initial therapy

The 2025 GOLD guidelines specify that GOLD groups should be used to guide initial therapy when treating a patient with COPD based on symptoms and exacerbation history in the prior year.[5] Use the GOLD guidelines summarized in the following algorithm to make the initial treatment decisions.

Figure 5: Algorithm for initial treatment in symptomatic patients with COPD[5]



Use one of two standardized tools to assess symptom severity

Modified Medical Research Council (mMRC) dyspnea score
Or ask: *"Do you walk slower than people of the same age because of breathlessness, or have to stop for breath on LEVEL ground?"*

COPD Assessment test (CAT)
Assesses overall health, not just dyspnea

Significant symptoms are an mMRC ≥ 2 or a CAT score ≥ 10.

*Establish exacerbation history: Exacerbations are discrete episodes of worsening symptoms (i.e., increased dyspnea, sputum volume, or purulence) over < 14 days that require intervention.

Evidence for initial use of inhalers in COPD

Rationale for starting LAMA or LABA monotherapy in early COPD

Three large long-term studies demonstrated the efficacy of long-acting bronchodilators for COPD: **UPLIFT**, **TORCH**, and **POET-COPD**. The **UPLIFT** trial showed that a LAMA was more effective than placebo. The **TORCH** trial showed that a LABA was more effective than placebo, and the **POET-COPD** trial found that a LAMA was more effective than a LABA. Details of each trial follow.

The **UPLIFT** study (Understanding Potential Long-term Impacts on Function with Tiotropium) enrolled nearly 6,000 patients with COPD over age 40. Participants were permitted to use other respiratory medications except inhaled anticholinergic drugs and were randomly assigned to receive either tiotropium (n=2,987) or placebo (n=3,006), with a 4-year follow-up.[80]

While lung function (pre- and post-bronchodilator) was significantly improved with tiotropium compared to placebo throughout the trial, there were no significant differences between the two groups in the annual rates of decline of FEV_1 or FVC, either before or after bronchodilator use. Patients randomized to

tiotropium, however, had significantly fewer exacerbations compared to placebo (RR 0.86; 95% CI: 0.81-0.91). There were no significant differences between the groups in COPD hospitalization rates.

The **TORCH** study examined the effect of salmeterol/fluticasone propionate combination therapy and its individual components on the survival of patients with COPD.[81] **TORCH** enrolled 6,112 patients with moderate-to-severe COPD and randomly assigned them to treatment with:

- salmeterol/fluticasone propionate (50/500 mcg)
- fluticasone propionate (500 mcg)
- salmeterol (50 mcg)
- placebo

Follow-up in the trial was 3 years, and the primary endpoint was all-cause mortality. Secondary endpoints were rate of exacerbations and health-related quality of life.[81] Table 3 summarizes results comparing the LABA salmeterol with placebo.

Table 3: TORCH results, salmeterol vs. placebo[81]

Outcomes	Effect Size
Annual rate of moderate or severe exacerbations	Salmeterol 0.97 vs. placebo 1.13 (HR 0.85; 95% CI: 0.78-0.93)
FEV_1 (post-bronchodilator)	Salmeterol -42 mL/year compared to -55 mL/year placebo ($p<0.001$)
Pneumonia rate Mortality rate Health-related quality of life score	No significant difference between salmeterol and placebo

The 1-year **POET-COPD** trial randomized 7,376 patients with at least one moderate or severe exacerbation in the prior year and FEV_1 ≤70% predicted to 18 mcg of tiotropium once daily vs. 50 mcg of salmeterol twice daily.[82] The time to the first exacerbation (the primary endpoint) was increased by 42 days with tiotropium compared with salmeterol (187 days vs. 145 days), corresponding to a 17% reduction in risk (HR 0.83; 95% CI: 0.77-0.90). The incidence of serious adverse events leading to the discontinuation of treatment was similar in the two study groups.

Rationale for combination therapy

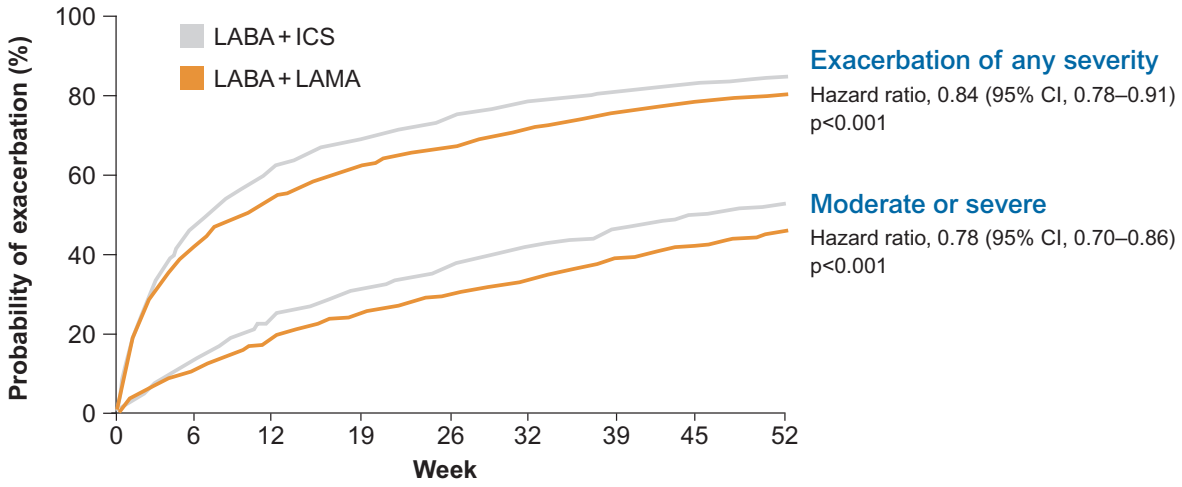
LABA + LAMA

A 2015 Cochrane review including 10 studies with 10,894 patients found that tiotropium (Spiriva) in combination with a LABA (including olodaterol, indacaterol, formoterol, and salmeterol) resulted in a modest improvement in lung function and quality of life as measured by the St. George's Respiratory Questionnaire (SGRQ) compared to either medication alone.[83] There was also a reduction in exacerbations with tiotropium (LAMA) added to a LABA, and insufficient evidence to determine risks and benefits of different LABAs.[83]

The combination of a LABA plus a LAMA was evaluated in the **FLAME** trial, which randomized 3,362 COPD patients with at least one moderate or severe exacerbation in the prior year and moderate to severe COPD for 52-weeks to either LABA + LAMA or LABA + ICS.[84] The LABA + LAMA combination resulted in an 11% decrease (3.59 vs. 4.03, RR 0.89; 95% CI: 0.83-0.96) in all exacerbations – including mild exacerbations not requiring treatment - and a 17% decrease in moderate to severe exacerbations

(RR 0.83; 95% CI: 0.75-0.91). Differences in lung function and quality of life measures also favored LABA + LAMA.

Figure 6: Probability of exacerbation in the FLAME trial[84]



Evidence for triple therapy

The **IMPACT** trial enrolled 10,355 patients with COPD who had a CAT score ≥10 and either an FEV_1 <50% predicted with one or more severe exacerbations in the prior year or an FEV_1 50-80% predicted with at least two moderate or one severe exacerbation the prior year. Patients were randomized to one of three once-daily treatment regimens:[74]

- triple therapy with the LABA vilanterol (25 mcg), the LAMA umeclindinium (62.5 mcg), and the ICS fluticasone furoate (100 mcg)
- dual therapy with fluticasone furoate (100 mcg) and vilanterol (25 mcg)
- dual therapy with umeclidinium (62.5 mcg) and vilanterol (25 mcg)

The rate of moderate or severe exacerbations with LABA + LAMA + ICS triple therapy (i.e., Trelegy, Breztri) was 0.91 per year vs. 1.07 per year with fluticasone furoate/vilanterol (RR 0.85; 95% CI: 0.80-0.90) vs. 1.21 per year in the umeclidinium/vilanterol group (RR vs. triple therapy 0.75; 95% CI: 0.70-0.81). There was a substantially higher incidence of pneumonia in the inhaled-glucocorticoid groups than in the umeclidinium/vilanterol group.

An important feature of the IMPACT trial is that patients with asthma-COPD overlap, who are more likely to benefit from inhaled corticosteroids, were included.[85] Many patients were on inhaled corticosteroids at baseline prior to randomization, resulting in withdrawal of inhaled corticosteroids and potential predisposition to exacerbations in the LABA + LAMA group.[86] However, a post-hoc analysis of the IMPACT trial suggested that triple therapy was beneficial even for non-ICS users (though the benefit was reduced and not statistically significant for all types of exacerbations).[85] When compared to LAMA + LABA therapy, triple therapy was associated with a 29% reduction in moderate/severe exacerbations (p<0.001) among those on baseline inhaled corticosteroids and a non-significant 12% reduction in moderate/severe exacerbations (p=0.115) for those who were not on baseline inhaled corticosteroids. The benefits of triple therapy compared to LAMA + LABA therapy were evident for both subgroups in an analysis of severe

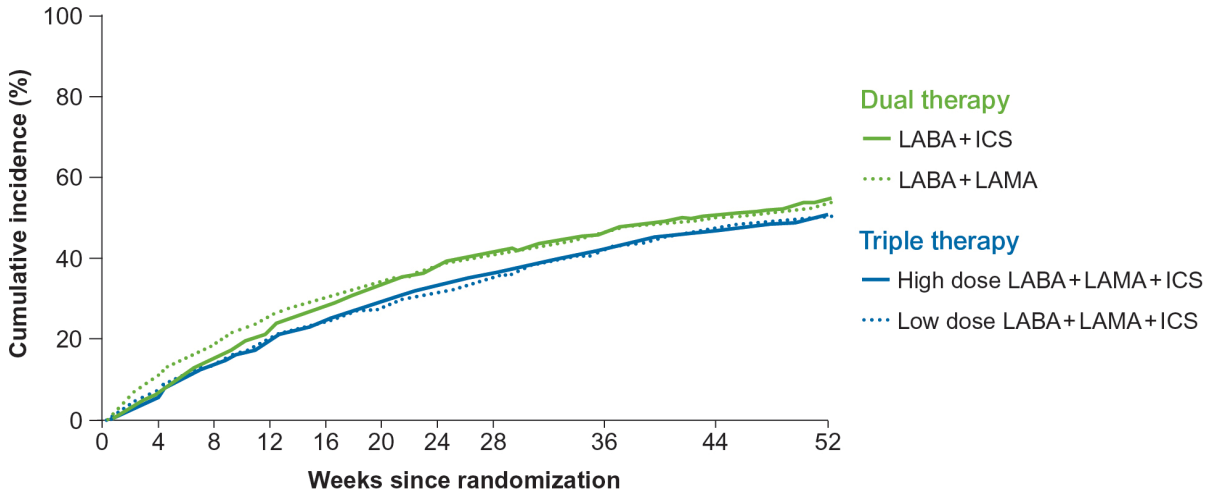
exacerbations: 35% reduction (p<0.001) for prior ICS users and 35% reduction (p=0.018) for non-ICS users.

The 2020 **ETHOS** trial evaluated the efficacy and safety of triple therapy at two ICS dosing levels in 8,509 patients with moderate-to-very-severe COPD and at least one exacerbation in the past year.[87] Patients with a diagnosis of asthma at the time of enrollment were excluded. Patients were randomized to one of four treatment arms:

- triple therapy with the LABA formoterol (9.6 mcg), the LAMA glycopyrrolate (18 mcg) and the ICS budesonide (320 mcg)
- triple therapy with formoterol (9.6 mcg), glycopyrrolate (18 mcg) and budesonide (160 mcg)
- dual therapy with formoterol (9.6 mcg) and glycopyrrolate (18 mcg)
- dual therapy with formoterol (9.6 mcg) and budesonide (320 mcg)

The annual rate of moderate or severe exacerbations was significantly lower with budesonide 320 mcg triple therapy compared to glycopyrrolate-formoterol (RR 0.76; 95% CI: 0.69-0.83), and also significantly lower compared to budesonide/formoterol (RR 0.87; 95% CI: 0.79-0.95). The benefit in terms of reduced exacerbations was similar, although somewhat less robust with 160 mcg budesonide triple therapy compared to the dual therapy arms: RR 0.75; 95% CI: 0.69-0.83 compared to glycopyrrolate/formoterol, and RR 0.86; 95% CI: 0.79-0.95 compared to budesonide/formoterol. The incidence of pneumonia was higher in the groups that received an ICS (3.5% to 4.5%) versus the LAMA + LABA group (2.3%) (p<0.05 for all comparisons).

Figure 7: Time to first moderate or severe exacerbation in ETHOS[87]



Role of ICS in initial therapy

The GOLD guidelines (both for initial therapy and adjustment of therapy) reserve inhaled corticosteroids for only a specific subset of patients with COPD, due to increased risks such as pneumonias and thrush with ICS. However, roughly 70% of patients with COPD who lack a history of frequent exacerbations receive an ICS as part of their initial therapy, even after coexisting asthma is excluded, suggesting misuse of this treatment modality.[88,89] The algorithms provide specific cutoffs regarding the number of

exacerbations and/or the peripheral eosinophil counts that may drive decisions to start inhaled corticosteroids (higher blood eosinophil counts correlate with better responses to ICS for reducing exacerbations).[5] More general considerations are summarized in Table 4. It is important to recognize, however, that data continue to emerge about who is likely to benefit (and who is unlikely to benefit) from initiation of inhaled corticosteroids.

Table 4: Factors to consider when initiating ICS treatment[5]

Strong support for use	Consider use	Against use
• History of hospitalization(s) for COPD exacerbations despite appropriate long-acting bronchodilator therapy • 2 moderate exacerbations per year • Blood eosinophils ≥ 300 cells/μL • History of or current asthma	• 1 moderate exacerbation per year • Blood eosinophils 100-300 cells/μL	• Repeated pneumonia events • Blood eosinophils < 100 cells/μL • History of mycobacterial infection

Monitoring therapy

Inhaler technique: an often-neglected aspect of treatment

Optimal therapy with any inhaled medication relies on both adherence and good inhaler technique. The management of COPD may require the use of multiple inhaled medicines, employing several types of inhaler devices. This complexity in the medication regimen has the potential to cause problems with administration and adherence, which underscores the essential role that allied health professionals such as nurses and pharmacists play in education and instruction about inhaler techniques.

Inadequate inhaler technique is common: a prospective observational study of 244 patients with COPD discharged from a hospital found appropriate use of inhaler procedures in only 23% of patients.[90] The elderly are particularly vulnerable to poor technique because of potential poor eyesight, tremor, or coordination difficulties. Cognitive impairment may further compromise a patient's ability to effectively use an inhaler. Some devices require a level of inspiratory capacity that may be unachievable in severe COPD. For example, dry powder inhalers (see Table 5 for a list of these inhalers) require a greater inspiratory flow to deliver medication to the lower airways than pressurized metered or soft mist inhalers. This can result in inadequate delivery particularly in older patients, women, and those with short stature or decreased forced vital capacity.[91]

Many patients benefit from using a metered dose inhaler (MDI) with a spacer, especially if severe disease is present. Spacers provide several advantages including:

- Helping ensure more medication reaches the lungs rather than being deposited in mouth or throat
- Reducing the need to precisely coordinate pressing the inhaler and inhaling, which can be difficult for older adults
- Minimizing the amount of medication in mouth and throat, thus lowering risk of local side effects

Nebulizers are as effective as MDIs with spacers and may be preferred by patients unable to use an MDI. Note that nebulizers and some medications used in nebulizers are covered by Medicare Part B as durable medical equipment rather than Part D (the outpatient prescription medication benefit). Patients should be advised to check if the supplier of their nebulizer participates in Medicare prior to ordering prescribed supplies.

Counseling the patient using the package insert, as well as physically demonstrating the device, can significantly improve inhaler technique.[92] Make sure that the patient can demonstrate appropriate technique to a health care professional at the time of consultation or dispensing. Inhaler technique may begin to decline within two months after patient education, so regularly reinforce correct technique.[93] Review inhaler use at the time of any exacerbation.

Text and video descriptions of how to use various forms of inhalers (MDI, spacers, dry powder and soft mist inhalers) can be found at qrco.de/ALA_inhalerteaching. Some data suggest that patients may prefer one device over another, and the dose of medication required may be affected by the specific delivery device. However, evidence is lacking that any one delivery mode is more effective than another.[94-97]

Inhaler device types

The four currently available device-types for inhaled medications are:

- metered dose inhalers (deliver medication as short burst using a propellant)
- dry powder inhalers (medication in form of inhaled powder)
- soft mist inhalers (generate a slow-moving fine mist using mechanical power without propellants)
- nebulizers (convert liquid medication into fine mist inhaled over several minutes)

Each type of device has pros and cons such as ease of use, requirements for inspiratory capacity, cost, portability, environmental impact, and potential for oropharyngeal deposition. These factors must be weighed when deciding which type to prescribe for a given patient.

Table 5: Inhaler device types

Inhaler class	Metered dose inhaler (MDI)	Dry powder inhaler	Soft mist inhaler	Nebulizers
LABA		• salmeterol (Serevent Diskus)	• olodaterol (Striverdi Respimat)	• aformoterol (Brovana) • formoterol (Perforomist)
LAMA		• aclidinium (Tudorza Pressair) • tiotropium (Spiriva HandiHaler) • umeclidinium (Incruse Ellipta)	• tiotropium (Spiriva Respimat)	• glycopyrrolate (Lonhala Magnair) • revefenacin (Yupelri)
ICS	• betamethasone (QVAR Redihaler) • ciclesonide (Alvesco) • fluticasone (Flovent HFA)[g] • mometasone (Asmanex HFA)	• budesonide (Pulmicort Flexhaler) • fluticasone (Arnuity Ellipta, Flovent Diskus)[g] • mometasone (Asmanex Twisthaler)		• budesonide (Pulmicort)[g]
LABA + LAMA	• formoterol + glycopyrrolate (Bevespi Aerosphere)	• formoterol + aclidinium (Duaklir Pressair) • vilanterol + umeclidinium (Anoro Ellipta)	• olodaterol + tiotropium (Stiolto Respimat)	
LABA + ICS	• formoterol + budesonide (Symbicort, Breyna)[g] • formoterol + mometasone (Dulera) • salmeterol + fluticasone (Advair HFA)[g]	• salmeterol + fluticasone (Advair Diskus, AirDuo RespiClick, Wixela Inhub)[g] • vilanterol+ fluticasone (Breo Ellipta)[g]		
LABA + LAMA + ICS	• formoterol + glycopyrrolate + budesonide (Breztri Aerosphere)	• vilanterol + umeclidinium + fluticasone (Trelegy Ellipta)		
Rescue inhalers	• albuterol HFA (Proventil, Ventolin)[g] • levalbuterol (Xopenex HFA)	• albuterol (ProAir Digihaler, ProAir RespiClick)	• albuterol + itpratropium (Combivent Respimat)	• albuterol[g] • levalbuterol (Xopenex) • ipratropium (Atrovent)[g]

g = generic available

Environmental harms of MDIs

The hydrofluroalkanes (HFAs) contained in roughly 90% of the metered-dose inhalers used in the U.S. have more than 1000 times the global warming potential of carbon dioxide.[98] The annual environmental impact of these HFAs is estimated to be roughly equivalent to the annual emissions of 550,000 automobiles.[99] Dry-powder and soft-mist inhalers have negligible emissions compared to metered-dose inhalers, but these may not be appropriate for frail adults who lack sufficient inspiratory forces. Some

manufacturers are developing non-HFA-based inhalers, but these are not yet available on the US market. Solutions to the problem of HFA-based inhalers lie beyond the scope of this review, but this issue is, nonetheless, important to recognize and understand.

Withdrawal of inhaled corticosteroids

Inhaled corticosteroids, alone or in combination, are associated with higher rates of oral candidiasis, hoarse voice, skin bruising, and pneumonia.[79] Given these risks, withdrawal of ICS may be desired in certain patients. Some studies have shown an increase in exacerbations and/or symptoms after ICS withdrawal, while others have not.

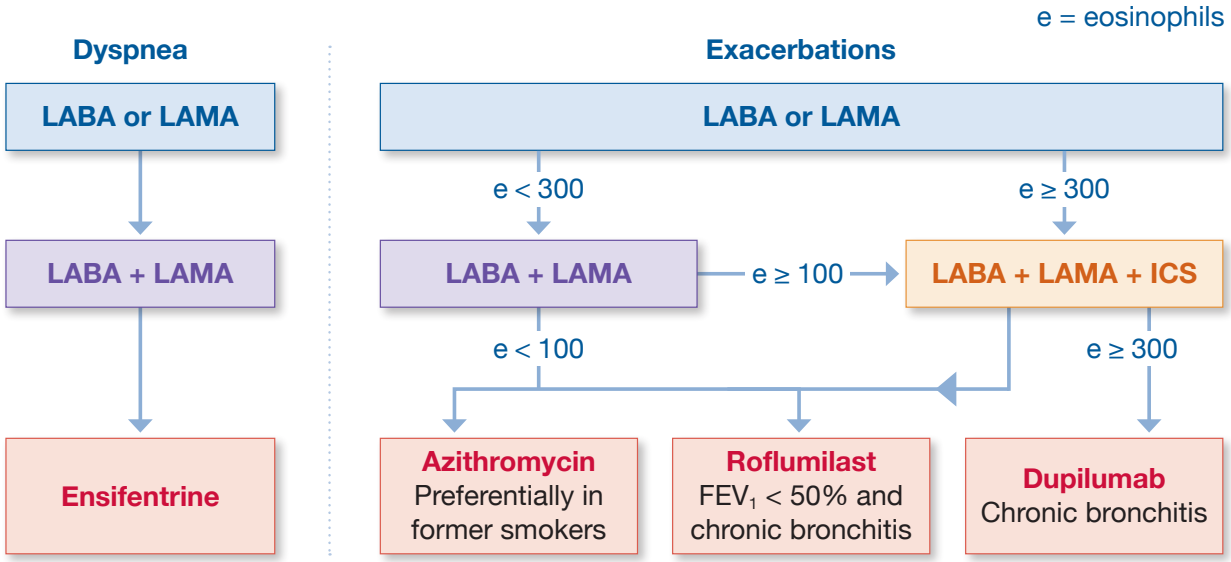
The largest trial, **WISDOM** (Withdrawal of Inhaled Steroids during Optimized Bronchodilator Management), enrolled 2,845 patients with COPD who had an FEV_1 <50% predicted and at least one exacerbation in the prior year. Patients were assigned to triple therapy (tiotropium, salmeterol, and fluticasone) during a six week run-in period and then randomly assigned to withdrawal of fluticasone in three steps over a 12-week period vs. continued triple therapy.[100] The time to first moderate or severe COPD exacerbation met prespecified noninferiority criteria (HR 1.06; 95% CI: 0.94-1.19), with no changes in dyspnea. There was, however, a slight decrease in lung function (between-group difference in FEV_1 43mL at week 52) with ICS withdrawal, and minor changes in health status.[100]

Exacerbations also did not increase following ICS withdrawal in the **SUNSET** trial, which evaluated de-escalation from long-term triple therapy (including an ICS) among 527 patients with COPD and an FEV_1 40-80% predicted without frequent exacerbations (no more than one moderate or severe exacerbation in the prior year).[101] Patients were randomized to continuation of their triple therapy or a change to indacaterol/glycopyrronium. The annualized rate of moderate or severe COPD exacerbations did not differ between treatments (RR 1.08; 95% CI 0.83-1.40). Adverse events were similar in the two groups. Inhaled corticosteroids withdrawal led to a statistically significant reduction in mean FEV_1 of -26 ml (95% confidence interval, -53 to 1 ml) at 182 days, although the clinically significance of this small difference is uncertain.

BOTTOM LINE: In patients who have mild COPD without an exacerbation history, a LAMA or LABA alone may reduce symptoms and prevent lung function decline. Most patients with more symptoms or an exacerbation history will require a LAMA + LABA. An ICS is used for initial therapy in patients who have blood eosinophils ≥ 300 cells/μL, a history of asthma, or a severe exacerbation history. Optimal therapy with any inhaled medication requires both adherence and good inhaler technique.

Escalating care for persistent dyspnea or COPD exacerbations

Figure 8: GOLD algorithm for increasing or non-responsive dyspnea/exacerbations

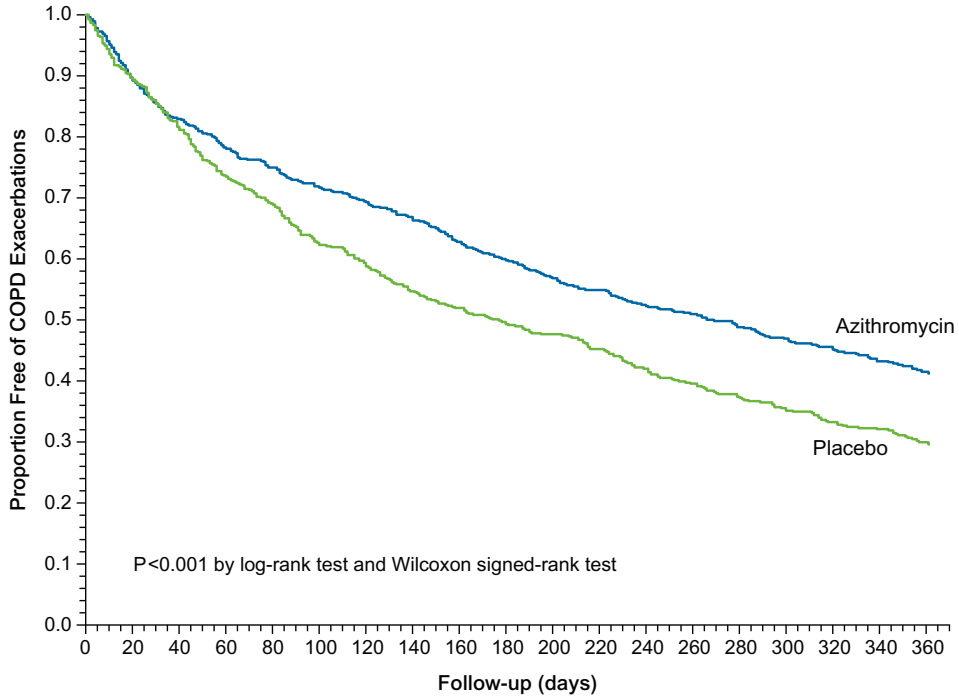


Macrolide antibiotics

The 2025 GOLD guidelines state that long-term therapy with azithromycin or erythromycin reduces exacerbations in patients with stable COPD, and that such therapy may be particularly helpful in former smokers with exacerbations.[5] The guidelines note, however, that treatment with azithromycin is associated with an increased incidence of bacterial resistance and hearing impairment.

A study in which erythromycin was given at 250 mg twice daily to patients with COPD for 12 months found a 35% reduction in the rate of moderate or severe exacerbations compared to placebo.[102] Patients treated with erythromycin had shorter duration of exacerbations compared with placebo. There were no differences in FEV_1 between the antibiotic and placebo groups.[102]

Figure 9: Patients without acute COPD exacerbation on azithromycin vs. placebo[103]



Proportion of participants free from acute COPD exacerbations for 1 year, according to study group. Acute exacerbations were experienced by 57% of patients in the azithromycin group and 68% of patients in the placebo group.

A 2011 clinical trial randomized 1,142 patients at high risk of exacerbation to azithromycin 250 mg daily for 1 year or placebo.[103] Comparing azithromycin to placebo, exacerbations occurred less frequently (1.48 vs. 1.83 per year, p=0.01), median time to first exacerbation was longer (266 vs. 174 days, p<0.001), and the rate of exacerbations was lower (57% vs. 68%). This effect was additive to other therapies for COPD, since >80% of patients were taking an ICS, a LABA, a LAMA, or a combination of these treatments. In pre-specified subgroup analyses, former smokers had a statistically significant benefit with azithromycin therapy compared to placebo, while current smokers did not. There was no difference in mortality between placebo and azithromycin groups.

Possible concerns regarding long-term macrolide therapy include hearing loss, potentially fatal QTc prolongation, and the development of antibiotic resistance.[104,105] Long-term azithromycin treatment should be reserved for patients with continued exacerbations despite an optimal regimen of other therapies for COPD and after a discussion of the risks and benefits of chronic antibiotic administration. All treated patients should be monitored with audiology testing and regular EKGs, and concomitant medications should be reviewed to ensure the patient is not using other medications (e.g., sotalol, haloperidol, fluoxetine, digoxin) that increase the risk of QTc prolongation.[106,103,107]

Phosphodiesterase-4 and phosphodiesterase-3 inhibitors

Phosphodiesterase (PDE) inhibitors have some clinical efficacy in the management of moderate-to-severe COPD. Inhibitors of the PDE_4 or PDE_3 isoenzymes have anti-inflammatory and bronchodilatory properties in the lungs.[108] Two PDE inhibitors are FDA-approved for reducing exacerbations in patients with COPD: roflumilast (Daliresp, an oral pill) and ensifentrine (Ohtuvayre, inhaled via nebulizer).

Potential PDE inhibitor side effects include diarrhea, nausea, reduced appetite, weight loss, sleep disturbances, and headache, although in some studies rates of adverse effects were similar to placebo.[109]

Roflumilast

Roflumilast (Daliresp) is a PDE_4 inhibitor given as a once-daily oral dose of 250 mcg for 4 weeks, then 500 mcg daily thereafter. A 2017 Cochrane meta-analysis of 13 trials (N=14,420) comparing roflumilast vs. placebo found a significantly reduced risk of having ≥1 exacerbation in the roflumilast group (OR 0.79; 95% CI: 0.73-0.86) as well as improved FEV_1 (mean difference 56.45 mL; 95%CI: 48.01-64.89 mL).[110]

Studies that included a comparator arm of bronchodilators also showed a benefit in exacerbation reduction. For example, the **REACT** study randomized subjects with severe COPD to roflumilast with ICS + LABA vs. placebo with ICS + LABA; background tiotropium was allowed.[111] The rate of moderate-to-severe exacerbations was 13% lower in the treatment group (0.81 exacerbations per patient per year vs. 0.93), though with higher withdrawal in the roflumilast group.

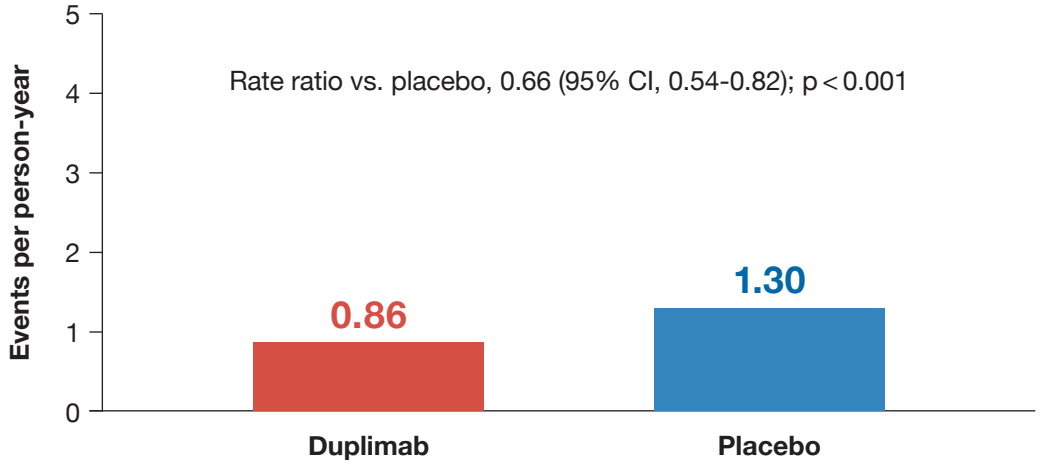
Ensifentrine

Ensifentrine (Ohtuvayre) was approved by the FDA in 2024 and is an inhibitor of both PDE_3 and PDE_4. It is delivered twice daily (3 mg doses) via a nebulizer. Parallel trials (ENHANCE-1 and ENHANCE-2) compared ensifentrine to placebo in patients aged 40-80 years with moderate-to-severe COPD. ENHANCE-1 (N=760) found that ensifentrine significantly improved FEV_1 after 12 hours and reduced the rate of exacerbations when compared to placebo (87ml; 95% CI: 55-119ml) as did ENHANCE-2 with 789 patients enrolled (94ml; 95% CI: 65-124ml).[112] Ensifentrine treatment also significantly improved symptoms (Evaluating Respiratory Symptoms) and quality of life (St. George's Respiratory Questionnaire) versus placebo at week 24 in ENHANCE-1 but not in ENHANCE-2. Adverse event rates in both trials were similar to placebo. To date, no trials have compared ensifentrine to roflumilast head-to-head.

Monoclonal antibodies

The 2025 GOLD guidelines cite strong evidence that the monoclonal antibody therapy dupilumab (Dupixent), which was the first biologic approved for COPD treatment, reduces exacerbations and improves lung function and quality of life in select patients.[5] Dupilumab is given as a 300 mg subcutaneous injection once every 2 weeks. The BOREAS clinical trial randomized 935 adults with exacerbation-prone COPD and blood eosinophil counts ≥300 cells/μL to either dupilumab or placebo and assessed responses in 6-12 months.[113] The rate of exacerbations was 0.86 events per person-year in the dupilumab group vs. 1.30 in the control group (RR 0.66; 95% CI: 0.54-0.82). The rate of adverse events was nearly identical in the two groups. In addition, prescribing information for dupilumab includes warnings (based on studies involving patients with dermatological conditions) for hypersensitivity reactions (e.g., anaphylaxis, urticaria) and ocular symptoms (e.g., conjunctivitis and keratitis).[114] Another monoclonal antibody, mepolizumab, was associated with a lower annualized rate of moderate or severe exacerbations when added to background triple inhaled therapy among patients with COPD and an eosinophilic phenotype in the 2025 **MATINEE** clinical trial.[115]

Figure 10: Rate of moderate or severe COPD exacerbation rate per person year[113]



BOTTOM LINE: For patients requiring more than bronchodilators and inhaled corticosteroids to manage COPD, selected antibiotics, phosphodiesterase inhibitors, or monoclonal antibodies may reduce the risk of exacerbations. Patient and disease factors drive the selection of one agent over another.

Managing acute exacerbations

Acute exacerbations present challenges to patients with COPD and their clinicians, and require strategies beyond maintenance therapy.[5] They can occur in any stage of COPD but are more common in moderate or severe disease.[116,117]

Exacerbations cause:[5]

- accelerated decline in lung function
- increased mortality
- hospitalizations
- reduced quality of life
- significant economic and social burden

Between 3% and 16% of exacerbations require hospitalization,[13,118] and in severe episodes, mortality can be as high as 10%.[119] Up to 24% of patients who require admission to an intensive care unit for a COPD exacerbation will die of causes related to the exacerbation.[117] The prevention and treatment of exacerbations is thus a major objective of COPD management.[5]

Etiology

The main causes of COPD exacerbations include:[5]

- bacterial infections
- viral infections (rhinoviruses, influenza, parainfluenza, respiratory syncytial virus, adenovirus, and coronaviruses)
- atypical organisms (*Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella*)
- cold weather
- pollutants (tobacco smoke, ozone, particulates, sulfur dioxide, nitrogen dioxide)
- other disease events (e.g., myocardial infarction, pulmonary embolism)

Exacerbations occur more frequently during winter.[5] Factors that increase the risk of severe exacerbations include increasing frequency of exacerbations, altered mental status, low BMI (20 kg/m^2 or less), marked increase in symptoms or changes in vital signs, medical comorbidities, poor activity levels, poor social support, severe baseline COPD, underutilization of home oxygen therapy, and poor inhaler technique.[13,120,121]

Diagnosis

Early diagnosis and prompt management of exacerbations may protect patients from functional deterioration and prevent hospital admissions.[5] The presenting symptom of increased dyspnea may be accompanied by increased cough and sputum production, wheezing, chest tightness, or change of sputum color. Non-specific symptoms such as fever, malaise, insomnia, sleepiness, fatigue, depression, and confusion may occur but are not diagnostic for an exacerbation.

The assessment of an exacerbation is based on symptoms, functional status before the exacerbation, and, potentially, arterial blood gas measurements and a chest X-ray. For test results, acute changes from baseline are more clinically relevant than absolute values. In patients with severe COPD, a change in mental alertness signals a need for immediate evaluation.[5]

An increase in sputum purulence (i.e., color) may suggest a bacterial cause.[122] It can be difficult, however, to determine a specific etiology because many microorganisms in sputum during exacerbations may also be present during periods of stable COPD.[123] Exacerbations may also result from the acquisition of new strains of existing bacteria. Sputum cultures are not routinely performed nor recommended in primary care.[123]

Differential diagnoses for worsening symptoms in a patient with stable COPD include:[5]

- pneumonia
- pneumothorax
- pleural effusion
- pulmonary embolus
- pulmonary edema
- coronary artery disease
- arrhythmia

Hospitalization

Hospitalization may be necessary if a patient has a marked increase in symptom intensity, such as sudden onset of resting dyspnea, increasing use of accessory muscles of respiration, onset or worsening of physical signs (e.g., cyanosis, peripheral edema), or acute confusion or other change in mental state.

Bronchodilators

First-line management for dyspnea in an exacerbation should begin with a SABA or SAMA. Administering bronchodilators with a nebulizer has no clear advantage over an MDI at equivalent doses in patients able to correctly use these devices,[96] although because few patients know how to use an MDI when they are acutely ill, GOLD specifically recommends nebulized bronchodilators in these situations.[5]

Titrate the dose interval according to clinical response, from hourly to every six hours. If monotherapy fails to adequately control symptoms, albuterol can be combined with ipratropium. Patients should initiate increased bronchodilator therapy at home and seek medical assistance if these measures do not control symptoms. Continue long-acting bronchodilators during an exacerbation; if not previously used, consider initiating them as soon as possible.

Corticosteroids

The role of systemic corticosteroids (primarily prednisone and methylprednisolone) in the treatment of exacerbations is well established, as they can reduce the severity of an episode and speed recovery.[5]

A 2014 Cochrane review found that short-term (i.e., median 14 days) treatment of exacerbations with oral or parenteral corticosteroids:[124]

- significantly reduces the risk of treatment failure
- reduces the need for additional medical treatment
- shortens hospital stay
- improves lung function and reduces dyspnea
- increases risk of an adverse drug event

The **REDUCE** trial, in which a course of 40 mg prednisone daily was given for either 5 or 14 days for an acute COPD exacerbation, found that 5-day treatment was non-inferior to 14-days for repeat exacerbations and time to a next exacerbation.[125] A 2018 Cochrane review including this study and others concluded that five days is sufficient;[126] in general, prednisone 40 mg/day for 5 days is recommended.[5] Tapering of corticosteroid therapy is not necessary after short-term administration.

Chronic treatment with systemic corticosteroids should be avoided because of an unfavorable benefit-to-risk ratio.[5] Such use confers a substantial risk of adverse effects such as weight gain, osteoporosis, cataract development, and hyperglycemia.[123] In an outpatient setting, inhaled corticosteroids should be continued during an exacerbation, and, if not previously used, should be considered in order to reduce the risk of further exacerbations.[5,125]

Antibiotics

Many patients with acute COPD exacerbations are treated with antibiotics, but the value of antibiotics is relatively modest, except in the ICU setting where meta-analyses show a strong beneficial effect, according to a 2018 Cochrane review of 19 trials with 2,663 patients.[127] For outpatients with mild to

moderate exacerbations, low-quality evidence suggests that antibiotics reduced the risk for treatment failure between seven days and one month after treatment initiation (RR 0.72; 95% CI: 0.56-0.94). One trial in outpatients suggested no effects of antibiotics on mortality.[127] Only one trial (n=35) evaluated health-related quality of life but did not show a statistically significant difference between treatment and control groups.[127]

Evidence of moderate quality from the Cochrane review does not support the use of antibiotics among inpatients with severe exacerbations (excluding ICU patients), with no beneficial effects of antibiotics on mortality in two trials but a large improvement in mortality in another, smaller trial.[127]

Patients most likely to benefit from antibiotic therapy for an exacerbation are those with moderate to severe disease with increased sputum purulence (color), increased sputum volume, and/or increased dyspnea.[5] New evidence suggests that acute phase reactants, such as C-reactive protein (CRP) and procalcitonin, may have a role to play in guiding antibiotic prescribing during COPD exacerbations.[128]

Appropriate antibiotic prescribing is based on the pathogens that are most common in COPD exacerbations and is guided by previous sputum cultures and/or local resistance patterns.[5] Since bacterial colonization is common in patients with COPD, sputum cultures during exacerbations are not clinically useful to guide therapy. Oral antibiotics such as doxycycline or macrolides are recommended as first-line treatment in patients exhibiting increasing sputum volume and purulence, while quinolones or ampicillin plus clavulanate are considered for patients with repeated exacerbations, suspected or confirmed bacterial resistance based on prior cultures, or certain risk factors (e.g., bronchiectasis).[91]

A response to antibiotic therapy is usually seen within 3-5 days. A 2008 meta-analysis of 21 studies (10,698 patients) found that a short course of antibiotic therapy (≤5 days) was as effective as a longer course, regardless of antibiotic class, in patients with mild to moderate exacerbations of chronic bronchitis and COPD.[129] Most of the studies included in the meta-analysis were conducted in the community.[129]

Exacerbation self-management

Selected patients at risk of COPD exacerbations and who can reliably self-manage medications, should be encouraged to:[130]

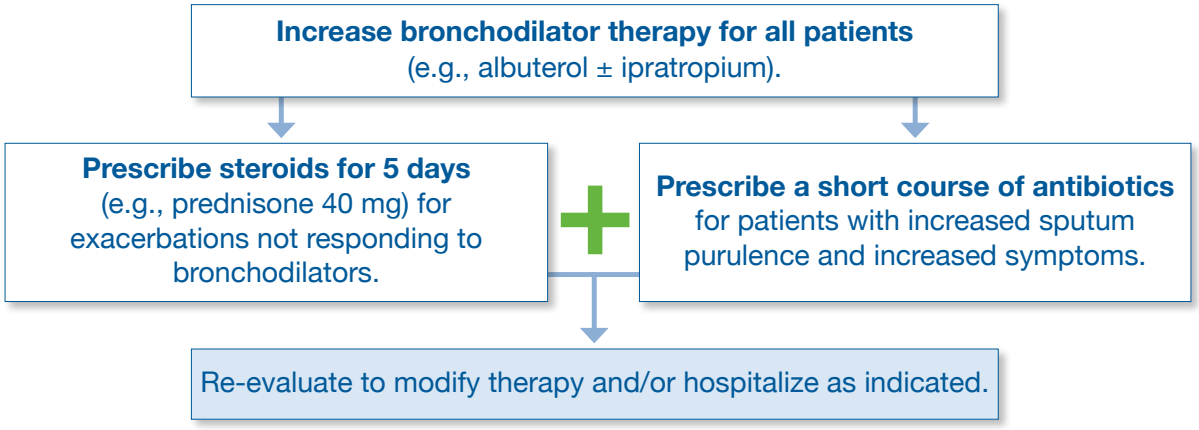
- increase their bronchodilator therapy as appropriate to control symptoms
- start an oral corticosteroid (e.g., prednisone 40mg daily x 5d) if increased breathlessness interferes with activities of daily living
- begin antibiotic therapy (e.g., azithromycin)

Such patients should be educated about when to begin an oral corticosteroid and/or antibiotic and have a supply of these agents at home so that initiation of therapy is not delayed. Patients should also be educated to seek medical advice if symptoms worsen despite additional therapy, particularly in the event of symptoms of a severe exacerbation (e.g., being very short of breath). A written “action plan” can be created in collaboration with a patient to help them recognize changes in symptoms and specify appropriate actions for managing their condition. The use of antibiotics and oral corticosteroids should be monitored.

A Cochrane review of COPD self-management interventions that include action plans for exacerbations (22 studies with 3,854 patients) found a lower risk of respiratory-related hospital admissions and improvements in health related quality of life in groups using such interventions compared to placebo.[130] No significant mortality benefit was observed.

Putting it all together: Managing exacerbations

Figure 11: Managing a COPD exacerbation in the outpatient setting[5]



BOTTOM LINE: COPD exacerbations accelerate the decline in lung function and pose a significant risk of short-term mortality. Therapy depends on the severity of symptoms, requiring use of short-term bronchodilators and possibly oral prednisone and antibiotics in selected patients.

Non-pharmacological interventions for COPD

Patient education about non-pharmacological interventions for COPD, delivered with attention to literacy levels and preferred language, can play an important role in improving functional status, increasing the ability to cope with COPD, and enhancing health status.

Immunization

The 2025 GOLD guidelines recommend that patients with stable COPD receive the following vaccinations to help reduce the risk of lung diseases such as pneumonia and/or COPD-related exacerbations:

- Respiratory syncytial virus vaccination
- Annual flu vaccine
- COVID-19 vaccine or boosters as available
- One dose of pneumococcal vaccine (either PCV21 or PCV20)
- Tdap vaccination for those not vaccinated in adolescence
- Zoster vaccination for those aged ≥50 years

Exercise

All patients with COPD can benefit from exercise training programs, which may improve muscle strength, exercise tolerance, dyspnea, and fatigue.[131] A 2016 meta-analysis (37 RCTs, 4,314 patients with COPD)

found that exercise training, alone or with activity counseling, significantly improved physical activity levels.[132] A relatively small (n=47) observational study found that a combination of strength training with either constant load or interval training resulted in better outcomes than either method alone.[133]

The main focus of exercise training is improving endurance of the leg muscles via walking, stationary cycling, and treadmill exercises. If able, patients should engage in endurance exercises to 60-80% of their symptom-limited maximum work or heart rate, although lower intensity exercise is also beneficial.[5] Exercise training can be enhanced by optimizing bronchodilator therapy before exercise sessions.[5]

Pulmonary rehabilitation

Pulmonary rehabilitation is a supervised exercise and strength training program during which patients also receive education about their disease. Pulmonary rehabilitation has not been linked to direct improvements in lung function, but has been shown to be the most effective therapeutic strategy to improve shortness of breath, health status, and exercise tolerance.[134] Pulmonary rehabilitation programs can also reduce anxiety and depression, reduce the frequency of exacerbations and hospitalization, and reduce mortality in some studies.[5] A Cochrane review found that pulmonary rehabilitation after an exacerbation reduced hospital admissions over 25 weeks (pooled OR 0.44; 95% CI: 0.21-0.91) and improved health-related quality of life using the St. George's Respiratory Questionnaire (SGRQ) (mean difference -7.80 points; 95% CI: -12.12 to -3.47 points) but did not reduce mortality.[135] Compared to non-frail older adults, frail patients who initiate pulmonary rehabilitation are twice as likely to be non-completers due to worsening disease, but those who do complete the program improve their frailty status.[136]

A 2020 retrospective cohort study in 197,376 patients with COPD found that initiation of pulmonary rehabilitation within 90 days of hospital discharge was associated with significantly lower risk of death over 1 year (absolute risk difference -6.7%; 95% CI: -7.9% to -5.6%; HR 0.63; 95% CI: 0.57 to 0.69.[137] Every 3 additional sessions was significantly associated with lower risk of death (HR 0.91; 95% CI: 0.85-0.98).

Despite the many advantages of pulmonary rehabilitation, fewer than 5% of people with COPD who might benefit actually receive it.[138,139] Current GOLD guidelines recommend pulmonary rehabilitation for all patients with relevant symptoms and/or a high risk for exacerbation.[5]

The most common model for pulmonary rehabilitation is a multidisciplinary, hospital-based outpatient program, but programs are also offered in community-based settings. Many programs include a psychosocial component because anxiety and depression are common in patients with COPD.[5] In-person home-based rehabilitation can be as effective as outpatient, hospital-based rehabilitation.[140] Virtual rehabilitation programs may be an effective alternative to in-person programs. A secondary analysis of two RCTs evaluating different modalities of pulmonary rehabilitation found no differences in outcome between in-person center-based rehabilitation and virtual home-based rehabilitation.[141]

Pulmonary rehabilitation is not recommended for patients with unstable cardiac disease.[142] Evaluation for ischemic heart disease with a stress test is advisable before most COPD patients start a new exercise program. Other pre-program assessments conducted by a pulmonary rehabilitation program may include spirometry, assessment of exercise capacity with the 6-minute walk test and a health-related quality of life test such as the Chronic Respiratory Disease Questionnaire (CRQ) or the SGRQ.[143]

Many rehabilitation programs involve 2-3 supervised sessions per week, each lasting about 2 hours. Most run for 6-12 weeks; longer programs may provide additional and more durable benefits.[5] The benefits

gained during rehabilitation recede within months after program cessation if patients resume a sedentary lifestyle. Maintenance programs often include exercise classes that meet regularly. Many patients who complete pulmonary rehabilitation programs value the improvement in their condition and are successful in altering their lifestyle to maintain it. It is unclear, however, how best to maintain such benefits in the long term.[5]

Availability

Formal pulmonary rehabilitation programs are not available to many patients who could benefit from this therapy. Availability is particularly limited among lower-income, minority, and rural populations. However, clinicians may be able to prescribe several elements of a formal rehabilitation program based on the concepts above, and virtual pulmonary rehab programs exist.

Directories of pulmonary rehabilitation programs in the U.S. are available from the American Association of Cardiovascular and Pulmonary Rehabilitation (aacvpr.org/Program-Directory) and LiveBetter (livebetter.org/directory).

Nutrition

Weight loss and muscle wasting occur in 20-35% of patients with stable COPD, and contribute to increased mortality and morbidity.[24] Nutritional intervention can be helpful if BMI is less than 21 kg/m^2 and/or significant involuntary weight loss has occurred (>10% during previous 6 months or >5% in the past month). Interventions can include small frequent meals with energy-rich supplements throughout the day. Liquid carbohydrate-rich supplements are often better-tolerated than a fat-rich supplement of equal calorific value, but increasing energy intake in patients with severe COPD can be difficult. Nutritional supplementation is often recommended to such patients, but evidence for its efficacy is limited. An appetite stimulant such as megestrol may increase body weight, but the weight gain often consists of fat mass only, so such appetite stimulants are not generally recommended.[24,142] Combine nutritional support with exercise wherever possible.[24] Referral to a nutritionist may be helpful if a patient is unable to maintain a healthy weight.

Conversely, obesity is becoming increasingly common in COPD, and obesity some data suggest that obesity may worsen dyspnea and reduce functional capacity.[144] Paradoxically, however, overweight and mild obesity in patients with COPD are also associated in some studies with improved survival[145] and a slower decline in lung function.[146] At this time, best practices in managing obesity and COPD are unknown, but weight loss may help relieve dyspnea symptoms in some patients.[144]

Long-term home oxygen therapy

Long-term administration of oxygen (>15 hours per day) can reduce mortality in patients with severe resting hypoxemia (PaO_2 <55 mmHg),[147] though it may not improve survival in patients with less severe hypoxemia or in those with only nocturnal oxygen desaturations.[148]

Long-term oxygen should be started in patients with stable disease (i.e., a patient with hypoxemia as defined below that is not due to an acute exacerbation) and optimized inhaler or other therapies if they have:[149]

- PaO_2 ≤55 mmHg or SaO_2 ≤88% at rest
- PaO_2 of 55–59 mmHg or SaO_2 89% at rest with evidence of pulmonary hypertension, *cor pulmonale*, peripheral edema, polycythemia (hematocrit >55%), or impaired mental status

Long-term oxygen therapy may be considered even with PaO_2 ≥60 mmHg if patients have:

- exercise desaturation
- sleep desaturation not corrected by continuous positive airway pressure (CPAP)
- severe dyspnea responding to O_2

When titrating oxygen, the goal is to maintain SaO_2 >88%-90% during rest, sleep, and exercise.[24]

The evidence for benefit from long-term oxygen therapy is strongest for patients with more severe levels of hypoxemia or disease across multiple studies. The 1980 NOTT trial randomized 203 patients with severe hypoxemia and noted nearly half the mortality rate in the continuous oxygen group compared to the group receiving 12-hours of nocturnal oxygen only.[150] The 1981 MRC trial randomized 87 patients with irreversible airway obstruction and severe hypoxemia and found lower mortality (45%) in the group randomized to 15 hours of oxygen daily compared to the no-oxygen group (66%) 5 years later.[151]

More recently, the **REDOX trial** in 241 patients with severe hypoxemia compared oxygen therapy for 24 hours a day vs. 15 hours a day and found no significant difference in a composite outcome of hospitalization or death from any cause after one year of follow-up.[152]

The benefits of long-term oxygen are less clear for patients with less severe disease. The **LOTT (Long-Term Oxygen Treatment Trial)** evaluated patients with milder degrees of resting hypoxemia (89-93%) or moderate exercise induced desaturation (SpO2 ≤80% for ≥5 minutes and <90% for ≥10 seconds during a 6 minute walk) and did not demonstrate benefits in the primary outcome measure (a composite of death and first hospitalization) or secondary outcomes of quality of life, lung function, or exacerbations.[148] LOTT did not demonstrate a benefit for the primary outcome of death or first hospitalization, nor did it demonstrate consistent benefits in secondary outcomes such as quality of life or lung function between the two groups.

Some patients with mild hypoxemia may still benefit from supplemental oxygen, however. A Cochrane review found that patients with COPD can exercise longer and have less shortness of breath when using oxygen during exercise,[153] while a 2019 trial found no differences in exercise capacity or quality of life in 111 patients randomized to oxygen supplementation vs. room air.[154]

Noninvasive ventilation

A study of noninvasive ventilation with oxygen therapy 2-4 weeks after hospitalization found that patients with persistent hypercapnea or hypoxemia who received nightly noninvasive ventilation (median pressure 24 cm H_2O) had decreased time to readmission or death compared to patients not receiving ventilation (4.3 months and 1.4 months, respectively).[155] Noninvasive ventilation reduced the annual risk of readmission or death (absolute risk reduction 17%, 95% CI 0.1%-34%). Quality of life was significantly better in the noninvasive ventilation group for the first three months, with no difference in quality of life thereafter.

Outside of the immediate post-hospitalization phase, a 2013 Cochrane review of seven studies testing noninvasive ventilation in 245 patients with COPD found no consistent or significant effects on gas exchange, exercise tolerance, quality of life, lung function, or other outcomes.[156] Two studies from 2014 with approximately 200 patients each were not included in the Cochrane review and reported conflicting results.[157,158] Many trials did not assess for undiagnosed sleep apnea, which, when treated, improves survival and the risk of hospitalization.[5] The 2025 GOLD guidelines state that in patients with both COPD

and obstructive sleep apnea there are clear benefits associated with the use of CPAP to improve both survival and the risk of hospital admissions.[5] However, except for select patients with severe COPD and pronounced daytime hypercapnia and/or recent hospitalization, there is no clear role for routine use of non-invasive ventilation in the management of COPD.[5]

BOTTOM LINE: Immunize for respiratory infections (RSV, influenza, COVID, pneumococcal pneumonia, and pertussis), encourage exercise and adequate nutrition, and provide self-management education in all patients with COPD. Refer patients with more symptoms or recent exacerbation to pulmonary rehabilitation. Oxygen therapy confers mortality benefit in COPD patients with severe resting hypoxemia, but not in patients with moderate resting or exercise hypoxemia. Non-invasive oxygen therapy can reduce risk of readmission or death in the weeks following an episode of hospitalization.

Advancing disease

Advance care planning

Severe COPD can significantly reduce life span. It is important to know in advance what courses of action a patient would prefer in the event of respiratory failure and inability to ventilate. Addressing these issues proactively when a patient is stable can prevent confusion and inappropriate care when a crisis ensues.

Healthcare professionals and family members can help patients during stable periods of health by initiating discussions about values and healthcare goals, including the appointment of a healthcare proxy. Discussions should invite patients to consider preparing for a life-threatening exacerbation, offering information on probable outcomes of treatment options such as intubation, non-invasive ventilation, or comfort-focused care. Clinicians should try to ensure that patients' end-of-life wishes and advance care plans will be known and honored during subsequent care, whether at home, in a hospital, or in a nursing home.[5] See Appendix I for some specific suggestions about ways to initiate and execute conversations about serious illness.

A recent review of palliative and end-of-life care in COPD identified characteristics that should act as triggers for discussion of end-of-life care. These include FEV_1 <30% predicted, oxygen dependence, at least one hospital admission in the previous year for an exacerbation of COPD, heart failure or other significant co-morbidities, weight loss or cachexia, decreased functional status/increasing dependence on others, and age >70 years. End-of-life issues that patients with severe COPD may want to discuss with their doctors include:[159]

- diagnosis and disease process
- treatments for improving symptoms, quality of life, and duration of life
- prognosis for survival and for quality of life
- what dying might be like
- advance care planning for future medical care and exacerbations

Palliative care

Palliative care focused on providing relief from the symptoms and stress of a serious illness is not limited to end-of-life care and should be available to patients at all stages of COPD and individualized to the needs and preferences of the patient and family.[160] Effective palliative care focuses on the patient's defined goals, patient and family distress, and assistance with bereavement after the patient's death. At the end of life, patients need reassurance that their caregivers will stay involved and will not abandon them. Perceptions of suffering are highly individual and a comprehensive assessment should be made of physical, emotional, autonomy, communication, economic, and spiritual concerns and preferences.[24]

Patients with COPD qualify for hospice services if their prognosis is reasonably expected to be 6 months or less. There are many predictors of mortality in COPD, including the modified BODE index.[5] Hospice can provide symptom control and support, typically including durable medical equipment, visiting services (typically weekly), opioids for air hunger, spiritual & social work support for patients/family, 13 months of bereavement support, and some medications. Many episodes of worsening dyspnea in patients coming to the end of life can be adequately treated with appropriate hospice care.

Breathlessness is a common cause of suffering in people with advanced COPD and should be assessed routinely.[161] Low-dose, short-acting opioids may be considered for patients with end-stage COPD and refractory dyspnea.[162] A longitudinal study of 83 patients with chronic refractory breathlessness concluded that when treating breathlessness with once daily sustained release morphine, it should be titrated to effect, since inadequate dose may generate no response. After an initial response, further dose increases should not occur for at least one week.[163] Evidence for the use of benzodiazepines and supplemental oxygen (in the absence of severe hypoxemia) is lacking or inconsistent and they are not recommended for refractory breathlessness.[161]

Lung volume reduction and transplant

Surgical options for severe COPD are limited and may pose risk but may be appropriate for patients with severe COPD, predominantly upper lobe emphysema, or low exercise capacity post-rehabilitation.[6] Lung volume reduction involves either surgical removal or bronchoscopic deflation of damaged tissue in the upper lobes, allowing the remaining lung sections to expand and the diaphragm to function more normally. A randomized trial comparing this surgery with medical management found that, in patients with severe upper-lobe predominant emphysema and low exercise capacity, surgery improved survival. In other groups, surgery improved lung function, exercise capacity, and respiratory-related quality of life; though it also increased mortality in a subset of more severe patients, who are no longer offered this surgery.[164]

A search for less invasive means of lung volume reduction has led to several trials of bronchoscopic lung volume reduction using a variety of devices including endobronchial valves, which are now FDA-approved. Several of these have demonstrated significant improvements in lung function, exercise tolerance, and symptoms.[165]

Lung transplantation offers the only opportunity for severely disabled patients with COPD to resume normal daily activities, but the median survival rate after lung transplantation (~ 5 years) remains far below that associated with the transplantation of other solid organs.[166]

Putting it all together

COPD is common, often preventable, and treatable. PCPs can help prevent COPD by encouraging smoking cessation in all patients. A combination of behavioral and pharmacological therapy is more successful than either alone.

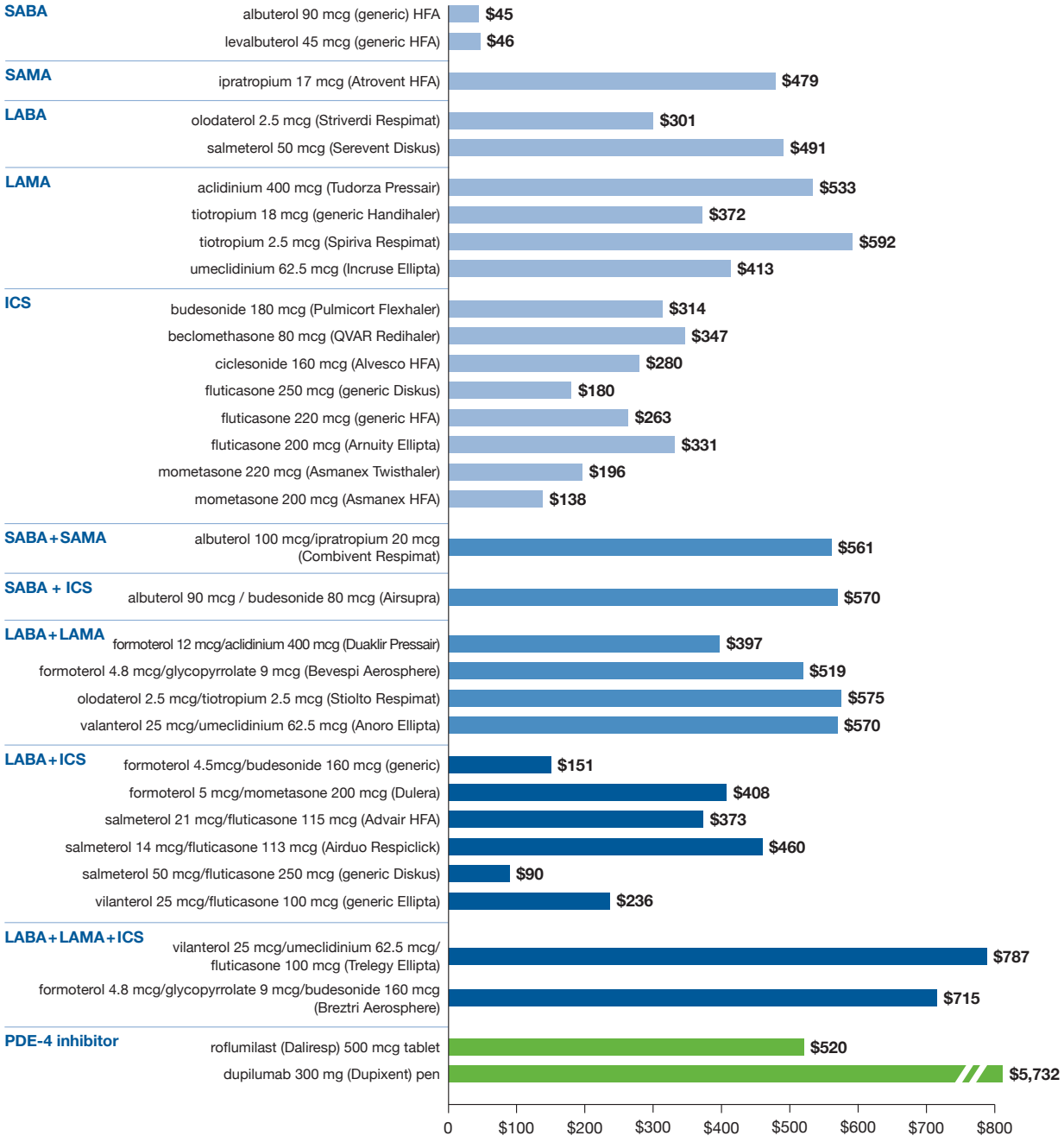
COPD should be suspected in any patient with respiratory symptoms and exposure to risk factors for the disease, particularly tobacco smoke. Diagnose COPD using spirometry before and after bronchodilator use (i.e., persistent FEV_1/FVC ratio <0.7), symptoms, and exposure to risk factors.

Treatment decisions are guided by severity of daily symptoms, exacerbation history, and blood eosinophils. Some patients on LAMA or LABA monotherapy, particularly those with more symptoms (e.g., unable to walk on a flat surface without stopping to catch one's breath) will require a step-up to combination LAMA + LABA therapy to control symptoms. Patients with ≥ 2 exacerbations/year and eosinophil counts above 300 cells/μL may benefit from the addition of an ICS, typically as part of a triple therapy regimen (ICS + LAMA + LABA).

Adjust therapy when needed, correcting inhaler use, and changing device type if needed. Deprescribe ICS in patients with recurrent pneumonia, lack of response to ICS, no clear indication, or long-term stability. Prevent exacerbations by recommending smoking cessation, routine vaccinations, and pulmonary rehabilitation, when indicated. Oxygen therapy confers mortality benefit in COPD patients with severe resting hypoxemia, with oxygen for 15 hours daily as beneficial as for 24 hours daily. Palliative care is not limited to end-of-life care and should be available to patients at all stages of COPD.

Costs of COPD medications

These are the 30-day list prices of the defined daily dose for each agent or combination product.



Not all inhalers are FDA approved to treat COPD.
Prices from a current market database, February 2025. Prices shown are for each individual inhaler or sufficient quantity of oral or injectable medication for a 30-day supply. These list prices are a guide; patient costs may be subject to cost-sharing arrangements set by insurers, coupons, and other incentives.

Appendix I

Suggestions for clinician dialog with COPD patients about advance care planning

Enable discussion

- "I'd like to talk about what is ahead with your illness and do some thinking in advanced about what is important to you so that I can make sure we provide you with the care you want—is that OK?

Assess understanding

- "What is your understanding now of where you are with your illness?"
- "How much information about what is likely to be ahead with your illness would you like from me?"

Share information

- "I want to share with you my understanding of where things are with your illness…"
- It can be difficult to predict what will happen with your illness. I hope you will continue to live well for a long time, but I'm worried that you could get sick quickly, and I think it is important to prepare for that possibility."
- "I wish we were not in this situation, but I am worried that time may be as short as ____ (express as range of days, weeks, or months)."
- "I hope that this is not the case, but I'm worried that this may be as strong as you will fell, and things are likely to get more difficult."

Explore possibilities

- "What are your most important goals if your health situation worsens?"
- "What are your biggest fears and worries about the future with your health?"
- "What gives you strength as you think about the future with your illness?"
- "What abilities are so critical to your life that you can't imagine living without them?"
- "If you become sicker, how much are you willing to go through for the possibility of gaining more time?"
- "How much does your family know about your priorities and wishes?"

Plan

- "I've heard you say that _____ is really important to you. Keeping that in mind, and what we know about your illness, I recommend that we _____. This will help us make sure that your treatment plans reflect what's important to you."
- "How does this plan seem to you?"
- "I will do everything I can to help you with this."

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Please rate your level of agreement with the following statements.

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1. The PACE academic detailer presented information to support smoking cessation.	5	4	3	2	1
2. The academic detailer discussed interventions to prevent exacerbations: immunizations, pulmonary rehabilitation, and inhaler technique assessment.	5	4	3	2	1
3. The academic detailer presented treatment intensification recommendations and the role of newer medications in treatment.	5	4	3	2	1
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About this publication

These are general recommendations only; specific clinical decisions should be made by the treating clinician based on an individual patient's clinical condition.

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