PACE Pharmaceutical Assistance Contract for the Elderly

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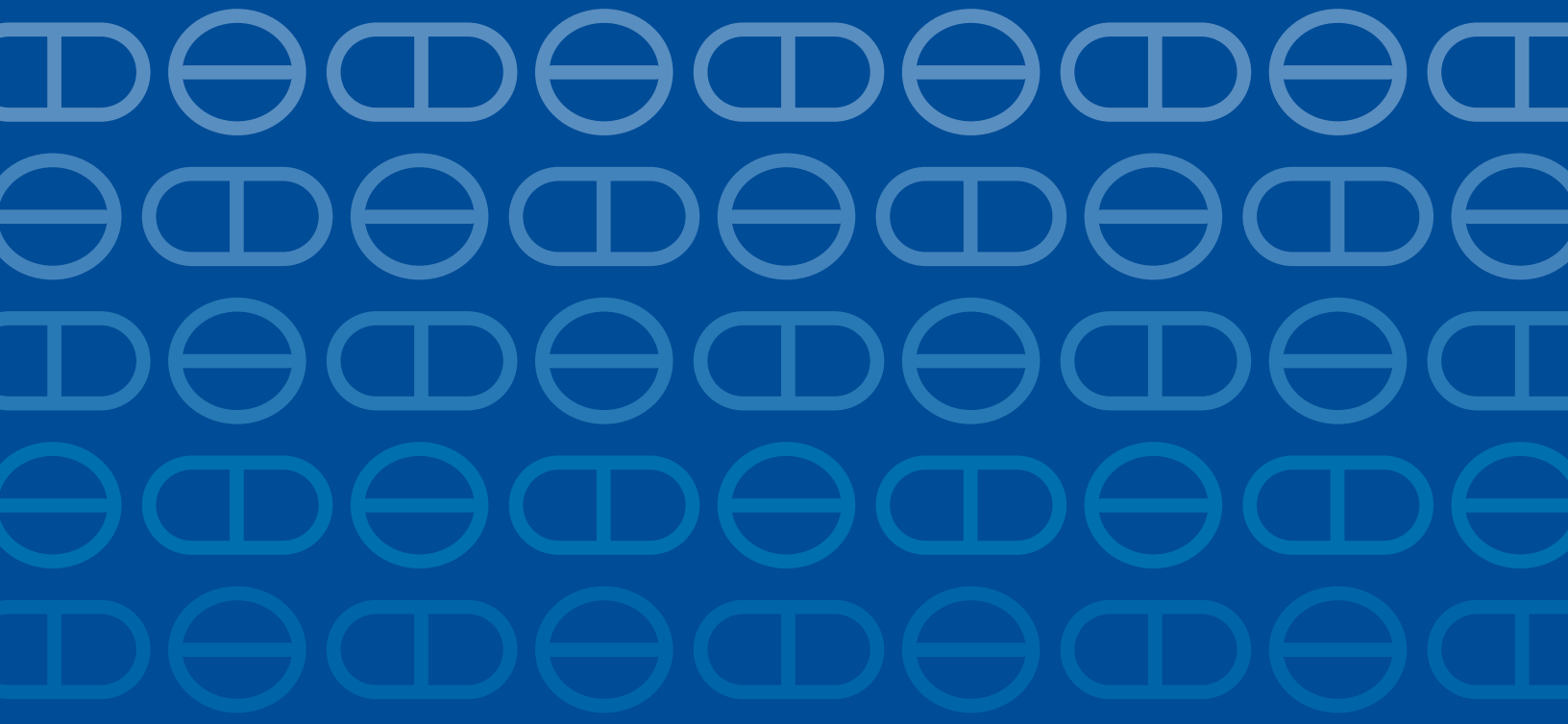
Helping patients with COPD breathe easier



Helping patients with COPD breathe easier

Integrating the latest evidence on chronic obstructive lung disease into primary care practice

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The Independent Drug Information Service (IDIS) is supported by the PACE Program of the Department of Aging of the Commonwealth of Pennsylvania.

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

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Accreditation:

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education and American Nurses Credentialing Center through the joint providership of Harvard Medical School and Alosa Health. The Harvard Medical School is accredited by the ACCME to provide continuing medical education for physicians and the ANCC to provide CNE credit hours to nurses.

Credit Designation:

The Harvard Medical School designates this enduring material for a maximum of 1.25 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This continuing nursing education activity was approved by ANA Massachusetts, an accredited approver by the American Nurses Credentialing Center's Commission on Accreditation. This activity was approved for 1.25 contact hours, of which 0.75 is eligible for pharmacology credit. Contact hours are awarded commensurate with participation and completion of the online evaluation and attendance attestation.

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 education program has several components, which include:

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

Its goal is to critically review and synthesize the most current clinical information on these topics into accessible, non-commercial, evidence-based educational material, to be taught interactively to providers by specially trained clinical educators.

Target Audience:

The educational program is designed for primary care physicians practicing internal medicine, primary care, family medicine, and geriatrics, and nurses and other health care professionals who deliver primary care.

Learning Objectives:

Upon completion of this activity, participants will be able to:

- Use spirometry data and clinical symptoms to identify and/or diagnose COPD

- Identify the GOLD group to select initial management strategy based on symptoms and history of exacerbations.
- Describe when an inhaled corticosteroid may be indicated and when it should be discontinued.
- For patients who smoke, assess their willingness to quit, and then tailor recommendations appropriate for their stage of readiness.
- Identify non-pharmacologic interventions, such as a regimen of exercise, good nutrition, and immunizations for all patients with COPD.
- Prescribe or recommend oxygen therapy for patients with chronic hypoxemia.
- Describe treatment of acute exacerbations with short-acting bronchodilators, systemic steroids, and antibiotics where appropriate.
- Instruct patients on proper use of inhalers and other inhalation devices.

Disclosure Policy:

Harvard Medical School has long held the standard that its continuing medical education courses be free of commercial bias.

In accord with the disclosure policy of the Medical School as well as standards set forth by the Accreditation Council for Continuing Medical Education, course planners, speakers, and content reviewers have been asked to disclose any relevant relationship they, or their spouse or partner, have to companies producing, marketing, re-selling or distributing health care goods or services consumed by, or used on, patients. In addition, faculty have been asked to list any off-label uses of pharmaceuticals and/or devices for investigational or non-FDA approved purposes that they plan to discuss. Such disclosure is not intended to suggest or condone bias in any presentation, but is elicited to provide the course director and participants with information that might be of potential importance to their evaluation of a given presentation.

Disclosures:

This material is provided by Alosa Health, a nonprofit organization which is not affiliated with any pharmaceutical company. No commercial support has been received for this activity. All individuals including planners, authors, reviewers, academic detailers, staff, etc., who are in a position to control the content of this educational activity have, on behalf of themselves and their spouse or partner, reported any financial relationships related to the content of this activity. The Independent Drug Information Service (IDIS) is supported by the PACE Program of the Department of Aging of the Commonwealth of Pennsylvania.

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Media used:

Printed educational material.

Instructions for Participation and Credit:

There are no fees to participate in this activity. To receive credit, participants must (1) read the statements on target audience, learning objectives, and disclosures, (2) study the educational activity, and (3) complete the post−test and activity evaluation. To receive *AMA PRA Category 1 Credit*™, or CNE nursing credit hours, participants must receive a minimum score of 70% on the post−test.

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The activity will take approximately 1.25 hours to complete.

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Please email any questions to **cme@alosahealth.org** or call **(617) 948-5997.**

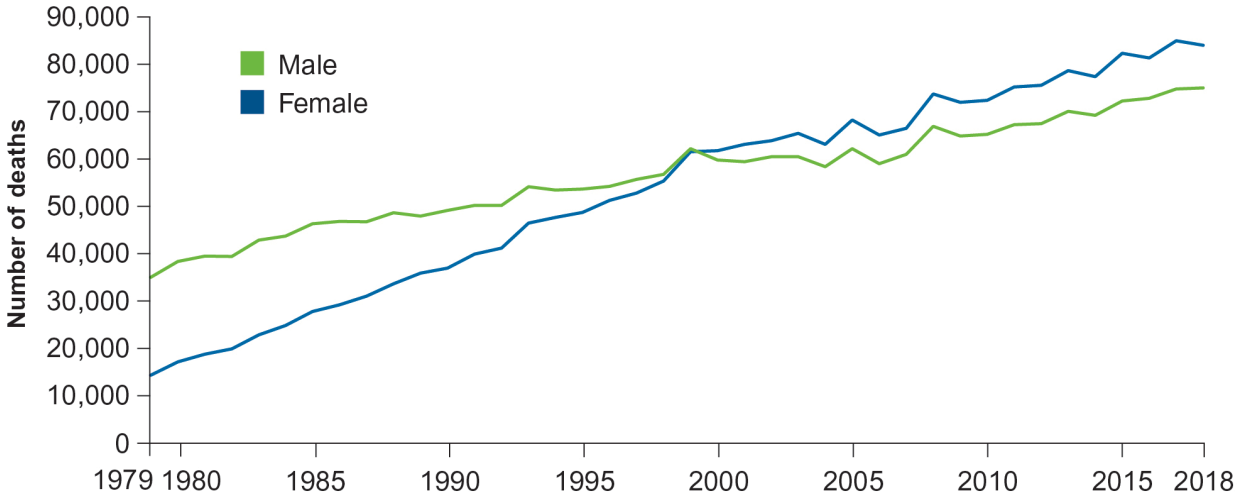
Table of Contents

The burden of COPD

Chronic obstructive pulmonary disease (COPD) is a significant national and global public health problem. It is the fourth-leading cause of death in the US, behind cancer, heart disease, and accidental injuries.[1] For the past decade, more women have died of COPD each year than men, a reversal of earlier trends (Figure 1),[2] which may be attributable to increased smoking among women relative to men and an increased susceptibility of female smokers to COPD.[3,4] Roughly 15.7 million Americans have been diagnosed with COPD, although the actual prevalence is much higher because many cases are undiagnosed until symptoms become severe.[5,6] In 2020 the total costs attributable to COPD are estimated at $49 billion in the US.[7] Between 50% and 75% of such costs result from exacerbations of the disease.[8]

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

Figure 1: Rise in COPD deaths by gender[2]



Pathophysiology

COPD, as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD), is a persistent, irreversible airflow limitation that is progressive and usually associated with exposure to noxious environmental stimuli.[9] It is characterized by dyspnea on exertion, wheeze, cough, and/or sputum production.[10]

Previous definitions of COPD emphasized chronic bronchitis and emphysema. 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 characterized by destruction of the alveoli and lung tissue, with subsequent loss of pulmonary elasticity.[11] Emphysema contributes to airflow obstruction, is an important phenotype for treatment and prognosis of COPD, and is

also easily 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.[12]

Asthma is a chronic inflammatory disease of the airways characterized by variable and recurring symptoms, with reversible airflow obstruction caused by bronchospasm. Although asthma and COPD both involve inflammation and airflow obstruction, they have important differences in pathogenesis, natural history, and presentation. The cells and mediators involved in the inflammatory process of asthma differ from those involved in COPD.[9] These differences explain why bronchodilators and inhaled corticosteroids (ICS) generally provide greater symptom relief for patients with asthma than for patients with COPD.

COPD results from pathological changes in the central airways, peripheral airways, lung parenchyma, and pulmonary vasculature. Macrophages, neutrophils, and T- and B-lymphocytes release inflammatory mediators that interact with cells in all these sites.[9] 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
- fibrosis and narrowing of smaller airways
- 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, which impairs gas exchange and leads to hypoxemia and hypercapnia
- hypoxic vasoconstriction of pulmonary arterioles, causing pulmonary hypertension[13]

Many COPD patients have some airflow limitation that can be ameliorated by bronchodilators, and some patients with chronic asthma develop irreversible airway narrowing. Because of this, t may not always be possible to perfectly differentiate between patients with asthma whose airflow obstruction does not remit completely and patients with COPD who have partially reversible airflow obstruction. The 2020 GOLD guidelines no longer use the term asthma-COPD overlap syndrome but note instead that asthma and COPD are different disorders, although they may share some common traits and clinical features (e.g., eosinophilia and some degree of reversibility).[9] Some other guidelines, by contrast, still refer to asthma-COPD overlap as a distinct clinical entity.[14]

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 likely are at risk early in life from reduced lung growth or early decline in lung function.[15,16] Among COPD patients, some have relatively stable lung function, and others have more rapid decline.[17] Exacerbations generally lead to deterioration in lung function,[18] worsening morbidity, more frequent hospitalizations, and reduction

in quality of life.[10,19] Progressive airflow limitation may lead to disability and early death, and differs from the reversible airway obstruction of asthma.

Risk factors for developing COPD

Factors contributing to the development of COPD include:[9,20]

- smoking
- occupational dust and fume exposure
- outdoor air pollution[21]
- exposure to biomass (e.g., wood, dung, straw) smoke from fires for cooking or heating[22]
- 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.[23] There is a close relationship between the amount of tobacco smoked and the rate of decline in FEV_1 (Forced Expiratory Volume in 1 second) although people vary greatly in their susceptibility to 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.[24] In susceptible smokers, cigarette smoking results in a steady decline in lung function, with a decrease in FEV_1 of 25-100 mL/year.[25] About 20% of COPD is attributable to occupational dust and fumes.[26] Urban/outdoor air pollution likely only accounts for a small percentage of COPD, although it may be a significant trigger for exacerbations.[21]

Systemic effects

Patients with COPD, particularly those with advanced disease, frequently have significant comorbidities.[9] Barnett et al., found that 82% of COPD patients had two or more additional conditions.[27] Westney, et al., analyzed patterns of COPD comorbidities in 291,978 adult COPD patients in a nationally representative Medicaid claims data set.[28] Acute care, hospital bed days, and total Medicaid-reimbursed costs increased as the number of comorbidities increased. The most prevalent comorbidities were hypertension (46%), diabetes (31%), affective disorders such as anxiety and depression (27%), hyperlipidemia (20%), and asthma (18%).[28]

Other common COPD comorbidities include:[28]

- osteoporosis and bone fractures
- loss of skeletal muscle mass and reduced muscle strength
- lung cancer
- sleep apnea
- gastro-esophageal reflux disease (GERD)
- aspiration
- ischemic cardiovascular disease

- congestive heart failure with reduced ejection fraction
- arrhythmias (e.g., atrial fibrillation, ventricular arrhythmia)
- impaired cognitive function
- anemia
- polycythemia

Predictors of mortality

FEV_1: 5-year survival is approximately 10% for patients with an FEV_1 <20% of the predicted normal value, 30% for those with FEV_1 of 20%–29% of predicted value, and 50% for those with an FEV_1 of 30%-39% of predicted value.[29]

Hyperinflation: the degree of hyperinflation as measured by inspiratory capacity divided by total lung capacity (IC/TLC) independently predicts all-cause and COPD mortality.[30]

Respiratory failure: the development of hypoxemic respiratory failure (partial pressure of arterial oxygen [PaO2]/fraction of inspired oxygen [FiO2] <300] or respiratory rate >24)[31] is an independent predictor of mortality, with a three-year survival rate of approximately 40%.[32]

Hypercapnia: patients with a partial pressure of arterial CO_2 ($PaCO_2$) >50 mmHg who are admitted to the hospital for a COPD exacerbation have a mortality rate of 11% during the hospital admission and 49% at 2 years.[33]

Body mass index (low and high), **degree of dyspnea,** and **frequency of acute exacerbations** also predict mortality and should be evaluated in all patients.[34]

BODE and e-BODE indices: BODE (body mass index, airflow obstruction, dyspnea and exercise capacity) and e-BODE (BODE plus exacerbations) predict mortality.[35,36]

Emphysema: Increased emphysema, as measured by computed tomography, is a risk factor for mortality.[37,38]

BOTTOM LINE: Include COPD in the differential diagnosis for any patient with dyspnea, wheeze, chronic cough, chronic sputum production, and/or history of exposure to risk factors for the disease, particularly tobacco smoke.

Identification and diagnosis

COPD is substantially under-recognized and can occur at an early age.[20] Early identification or diagnosis is important for prompt treatment, which may slow progression of the disease, improve pulmonary function, relieve symptoms, reduce the frequency of exacerbations, improve quality of life, and reduce morbidity and mortality.[9,39,40]

Medical history

When assessing a patient for COPD, the medical history should include:[9,34]

- 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, GERD, depression, and 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 (e.g., heart failure or degenerative joint disease). Assessment of exercise tolerance can allow for earlier detection of COPD in some patients.[41]

Table 1: Differential diagnosis of COPD[9]

Diagnosis	Suggestive features
Asthma	• Onset early in life (often childhood) • Reversible bronchoconstriction • Symptoms variable and recurring • History of allergies, rhinitis, and/or eczema • Family history of asthma
Heart failure	• Crackles on auscultation • Chest X-ray with dilated heart or pulmonary edema • Pulmonary function tests indicating restriction, with possible airflow limitation
Bronchiectasis	• Large volumes of purulent sputum • Commonly associated with bacterial infection • Crackles on auscultation • Chest X-ray/CT shows bronchial dilation, bronchial wall thickening
Tuberculosis	• Onset at all ages • Chest X-ray shows infiltrate • Hemoptysis • Microbiological confirmation • High local prevalence of tuberculosis, or history of travel to an endemic area
Obliterative bronchiolitis	• Onset at younger age • Nonsmoking status • May have history of rheumatoid arthritis or acute fume exposure • CT on expiration shows hypodense areas • Seen after lung or bone marrow transplantation

Diagnosis	Suggestive features
Diffuse panbronchiolitis	• Predominantly seen in patients of Asian descent • Most patients are male and nonsmokers • Almost all have chronic sinusitis • Chest X-ray and high-resolution computed tomography show diffuse small centrilobular nodular opacities and hyperinflation

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. Rhonchi may be heard, caused by air passing through bronchi narrowed by inflammation, spasm of smooth muscle, or presence of mucus in the lumen.[42]

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 (see more detail in the section on supplemental oxygen on page 31).[43]

Spirometry

Spirometry is required for the diagnosis of COPD and also provides prognostic information. It is the most reproducible, standardized, and objective way of measuring airflow limitation. Spirometry can sometimes be performed by physicians, nurses, or other healthcare team members in the office or it can be done in a pulmonary function testing laboratory (available in most hospitals or medical facilities). Note: in 2020, during the SARS-CoV2 pandemic, many practices and facilities have limited the use of spirometry and pulmonary function testing due to the risk of aerosolized droplets. In the setting of reduced availability of functional testing, it may be reasonable to initiate treatment for presumed diagnoses of COPD based on history and other testing, but spirometry and/or pulmonary function tests should be obtained as soon as safely possible to confirm potential COPD diagnoses.

Patients can have moderately impaired lung function before they develop significant symptoms, so spirometry can help detect early disease.[44] Conversely, many current and former smokers have respiratory symptoms but do not have COPD.[45]

The functional values assessed on spirometry include:

- **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 is 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.[9] 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 12% and 200 mL), are more likely to have asthma.[14] Distinguishing between COPD and asthma is important, as the treatment strategies for the two diseases differ.

The FEV_1/FVC ratio tends to decline with age, and thus 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 and independence of the measure from reference values.1 The GOLD grades of obstruction (all with $FEV_1/FVC < 0.7$) are as follows:[9]

- Mild; FEV_1 ≥80% predicted
- Moderate; 50% ≤ FEV_1 <80% predicted
- Severe; 30% ≤ FEV_1 <50% predicted
- Very Severe; FEV_1 <30% predicted

Note that these grades of obstruction based on spirometry are not the same as the A, B, C, D groups used to classify patients and guide treatment in GOLD guidelines beginning 2017 and beyond. Spirometric grade predicts population-level outcomes and is used in decisions for some non-pharmacologic therapies (such as lung volume reduction and transplant), while ABCD stage is based on symptoms and exacerbation history and is now used to guide initial pharmacologic management.[9] Figure 2 presents the airflow limitation observed in patients with COPD.

Figure 2: Volume-time curve of a patient with COPD[46]

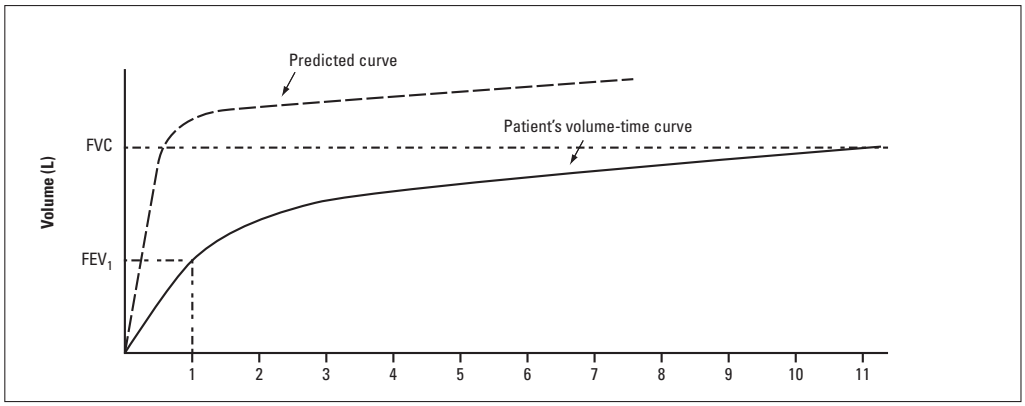


Figure 2. Volume-time curve of a patient with COPD. Airway obstruction is indicated by the significant straightening of the patient's curve compared with the predicted curve.

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

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[1] An alternative approach relies on the lower-limit of normal (LLN) based on the normal distribution of FEV_1 with the bottom 5% of the healthy population classified as abnormal. However, LLN values are dependent on the choice of valid reference equations using post-bronchodilator FEV_1, and there are not longitudinal studies available validating the use of the LLN, or studies using reference equations in populations where smoking is not the major cause of COPD.

Quantifying respiratory symptoms

Although quantification of airflow obstruction is very useful for the diagnosis of COPD, other factors will guide most treatment decisions. Symptoms including dyspnea, cough, sputum, exercise capacity, and the frequency of exacerbations provide evidence-based factors that can be used to determine treatment and prognosis. This is best done through the updated GOLD classification system for COPD (see below). 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.[47]

A similar, but even shorter, tool is the modified Medical Research Council (mMRC) dyspnea scale (Table 2).[9,48]

Table 2: mMRC dyspnea scale

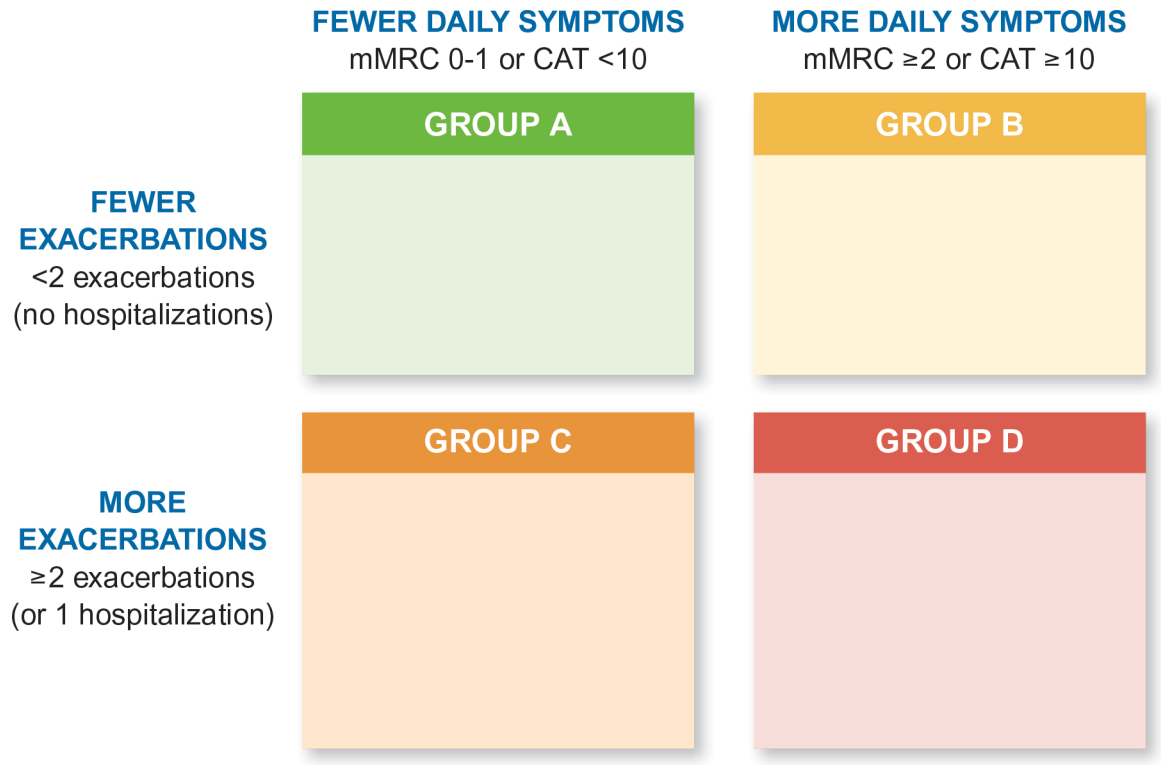
Grade	Description of breathlessness
0	I only get breathless with strenuous exercise
1	I get short of breath when hurrying on level ground or walking up a slight hill
2	On level ground, I walk slower than people of the same age because of breathlessness, or have to stop for breath when walking at my own 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

An mMRC score is one of the parameters in the GOLD COPD classification system (see below) and is also a parameter in the BODE Index, another prognostic tool for COPD. Currently either the mMRC or CAT score are necessary for assessing symptom burden under the GOLD guidelines, though the CAT may be superior as it assesses symptoms beyond just dyspnea.

COPD staging: The GOLD groups

The 2020 GOLD criteria use airflow obstruction as measured by spirometry only for diagnosis and prognosis (or to guide certain non-pharmacologic treatments), and use symptoms (classified by CAT or mMRC score) and the frequency of exacerbations to guide initial pharmacologic treatment decisions.[9] The GOLD groups are determined by the number of exacerbations in the previous year and daily symptom severity (Figure 3).

Figure 3: The GOLD classification system[9]



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.[49] Similar considerations apply for chest CT scans, though many COPD subjects 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 be the cause of respiratory symptoms in patients who develop COPD at a young age (<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 55 who do not have a substantial history of tobacco smoke or other environmental risk exposure. Testing should include measurement of serum alpha-1 antitrypsin levels, either coupled with or followed by genotyping or protein phenotyping.[50,51] 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.[34,52]

BOTTOM LINE: it may not be possible to completely differentiate patients with asthma whose airflow obstruction does not remit completely and patients with COPD who have partially

reversible airflow obstruction. Use spirometry to diagnose COPD and 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

Aggressive treatment can alter the natural history of the disease, and non-pharmacologic approaches may be particularly beneficial.[39] The goals of COPD management include:[9]

- relieving symptoms
- improving health status and quality of life
- improving exercise capacity
- reducing the number and severity of exacerbations
- identifying and treating exacerbations if they do occur
- preventing disease progression
- preventing and treating complications
- reducing mortality
- ensuring appropriate end-of-life planning and palliation

All patients with COPD benefit from the following interventions:[9]

- smoking cessation, including pharmacologic and behavioral therapy
- reducing exposures to occupational and environmental toxins
- exercise
- adequate nutrition
- self-management education, including proper inhaler use
- immunization

Patients with COPD may also benefit from the following:

- pulmonary rehabilitation
- evaluation and treatment of comorbidities
- medications
  - inhaled bronchodilators
  - inhaled corticosteroids
  - phosphodiesterase 4 inhibitors
  - chronic azithromycin
  - oral steroids and antibiotics for exacerbations
- supplemental oxygen
- lung volume reduction surgery
- bronchoscopic modes of lung volume reduction (e.g. endobronchial valves)
- lung transplantation
- palliative care

Patient education, 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. It can also be a key component in encouraging smoking cessation.[9]

The management of COPD is largely driven by symptoms, functional status, and the need to prevent exacerbations, since there is a poor correlation between the presence/severity of symptoms, exercise capacity, and the degree of airflow limitation on spirometry.[9] Similarly, changes in lung function after treatment with any drug are an imperfect guide to clinical response to therapy. Accordingly, frequent reassessment of the patient's global functional status and symptom control is the keystone of long-term COPD management.

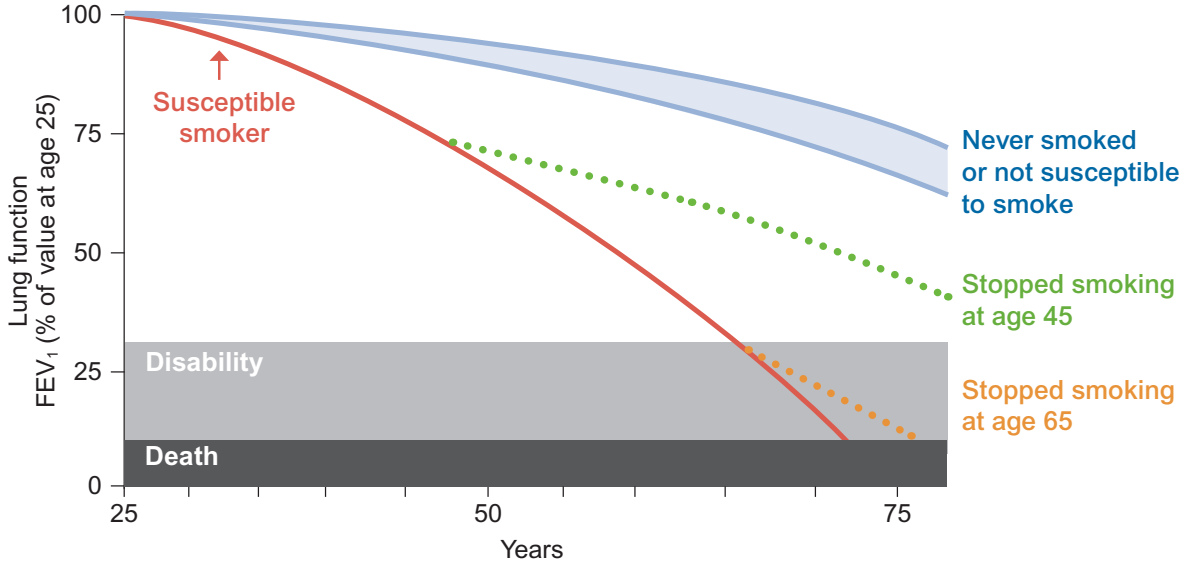
Spirometry should be performed whenever a significant worsening of symptoms or a major complication occurs. Spirometry in stable disease can provide useful information on the rate of decline in lung function and is recommended at least annually.[9]

Smoking cessation

Smoking cessation is the most effective single 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.[25,53] A 2008 systematic review found that stopping smoking slows the rate of lung function decline and improves survival, even in patients with severe COPD.[54] Smoking cessation also reduces the risk of exacerbations, with the magnitude of the reduction dependent upon the duration of abstinence.[55]

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[16,25]



Smoking cessation is thus a key intervention in all stages of COPD.[9,56] An evidence-based clinical practice guideline, *Treating Tobacco Use and Dependence: 2008 Update*, sponsored by the Department of Health and Human Services, describes useful approaches to this problem and provides information to help patients stop smoking. A link to this guideline may be found at AlosaHealth.org/COPD.

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":[57]

- *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

One conceptual model places patients who smoke at various stages of tobacco cessation:[58]

- pre-contemplative: NOT ready to make a commitment to quitting
- contemplative: considering quitting in the near future
- determination: ready now, may be planning a quit date themselves
- action: actively engaged in quitting
- maintenance: have abstained, but are at risk of relapse

If patients are in the pre-contemplative stage, review the 5 "Rs" with them:[59]

- Relevance: point out the effects of smoking on their *own* health: e.g., if they had a myocardial infarction, make sure they know smoking makes another more likely
- Risks: use their spirometry results to point out COPD if it is present; use a family history of lung cancer to emphasize their own increased risk
- Rewards: note the money saved on tobacco or health insurance plans, etc.
- Roadblocks: identify psychosocial stressors that drive smoking (e.g., depression)
- Repetition: keep reminding them of these potential motivators

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.[60,61] A successful tobacco cessation program might include the following:[62]

- Social support: presence of family/friends to enable the plan and identify social barriers that may hinder success (e.g., a smoking spouse)
- 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 psychiatric disease: smoking is more common in patients with depression, schizophrenia, and alcohol use disorder; often smoking cessation will be unsuccessful without treatment of 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/data_statistics/fact_sheets/cessation/quitting/index.htm

Providing brief advice about quitting smoking increases the likelihood that someone who smokes will successfully quit and remain a nonsmoker 12 months later. More intensive advice may result in slightly higher rates of quitting.[63] 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).[61]

Focused counseling sessions can have substantial effects, and can increase tobacco cessation success by up to 20%.[62] 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.[62] Phone follow-up by a non-MD provider is very useful.[64]

Medications to help with quitting

Good evidence suggests that the following pharmacotherapies can be effective to support smoking cessation, unless contraindications are present:[59]

- nicotine replacement therapy, including long-acting agents (transdermal patches) and short-acting agents (gum, lozenges, inhalers, and nasal spray)
- bupropion (a norepinephrine/dopamine reuptake inhibitor and nicotinic acetylcholine receptor antagonist)
- varenicline (a partial agonist of the alpha-4/beta-2 nicotinic acetylcholine receptor)

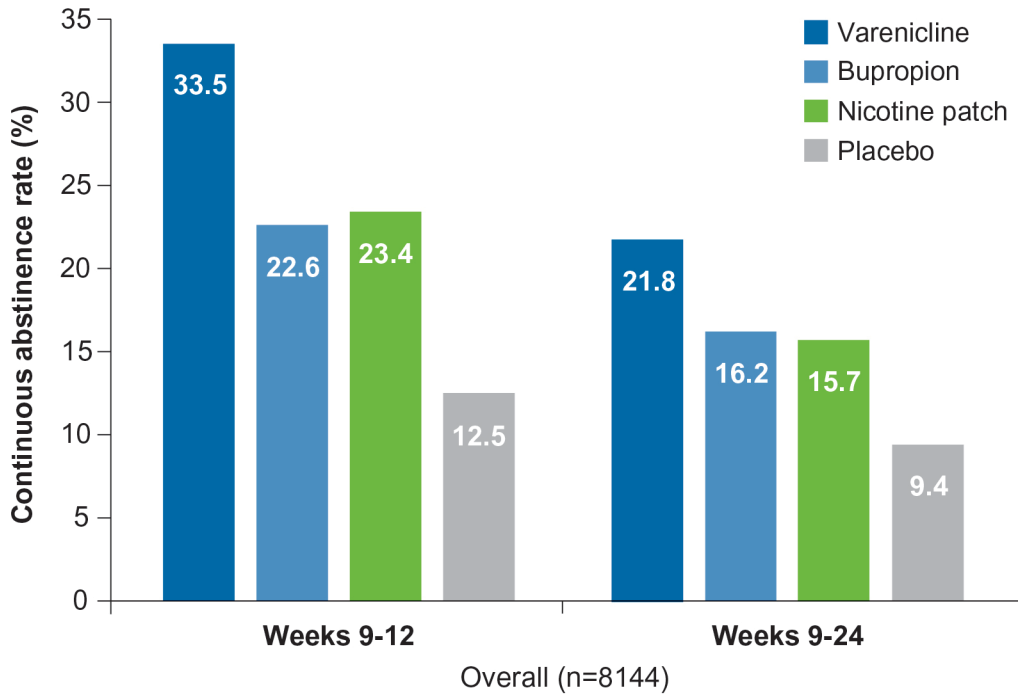
Varenicline (Chantix) was found to be superior to bupropion (Zyban, Wellbutrin, others) and a nicotine patch in EAGLES, the largest randomized trial to date comparing pharmacologic therapies for smoking cessation (Figure 5).[65] Varenicline (Chantix) was not compared to long-acting nicotine replacement in combination with short-acting agents. Other studies suggest that varenicline, bupropion, and nicotine replacement each have success rates of ~15-25%.[66-68] Nicotine replacement therapy (short- and long-acting) may be combined with either varenicline or bupropion to increase rates of success. Choose therapy based on patient preference, cost, and the presence of any mitigating medical and/or psychiatric conditions.

Some points to consider for each therapy:

- Nicotine replacement therapy[69,70]
  - 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 (a model that is analogous, for example, to the use of long and short acting insulin in type 1 diabetes mellitus).

  - There is no evidence of increased cardiovascular events with use after myocardial infarction.
- Varenicline[71]
  - To allow time for varenicline to take effect, a quit date should be set at least 1 week after starting the drug.
  - Neuropsychiatric side effects initially led to a black box warning in 2009; however, no significant risk was seen in meta-analysis including subjects with mental illness,[72,71] or in the EAGLES trial, in which approximately half of enrollees had stable chronic psychiatric disorders. The FDA subsequently withdrew this warning in 2016.[65]
  - Most evidence suggests minimal or no increased risk of cardiovascular complications in patients with stable cardiovascular disease.[73] 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.[74,75]
- Bupropion[76-78]
  - 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 can make bipolar disease (mania) worse.
  - There is an increased risk of seizure; avoid or use with extreme caution in patients at increased risk of seizures.
  - Evidence suggests that the drug is safe but not effective in patients discharged after ACS.[79]
- Combination therapy
  - Nicotine replacement in conjunction with varenicline is superior to varenicline alone.[80,81]
  - Likewise, 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.[82]

Figure 5: Abstinence rates from EAGLES trial of medications used in smoking cessation[65]



Alternative therapy for smoking cessation

Not enough data exist on which to base recommendations about the efficacy of acupuncture,[83] hypnosis,[84] mindfulness meditation,[85] or any other alternative therapy for smoking cessation. The use of e-cigarettes has been promoted by some as a tool for harm reduction and smoking cessation.[86] However, there is insufficient evidence from randomized controlled trials that e-cigarettes are superior to other FDA-approved agents or placebo.[87] Moreover, cases of vaping-associated lung injury continue to emerge.[9] Though most cases have been associated with THC-containing products, cases have also been reported among those using nicotine-containing products alone.[88] Therefore, e-cigarettes are not currently recommended for smoking cessation.[9]

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. A comprehensive approach to smoking cessation that combines behavioral therapy with pharmacological therapy is more successful than either mode of therapy alone.

Pharmacologic therapy for stable COPD

Bronchodilators

Bronchodilators are the cornerstone of drug treatment for COPD. 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.[9,29] Bronchodilators help reduce hyperinflation, thereby increasing inspiratory capacity, relieving dyspnea, 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, which increases cyclic AMP and produces functional antagonism to bronchoconstriction.[9] 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.[9]

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 newer generics and authorized generics) and levalbuterol (Xopenex HFA, generic), while SAMAs include ipratropium (Atrovent HFA). Both may be used intermittently to relieve worsening of 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 short-acting ß-agonists have equal efficacy to short-acting anticholinergics in COPD.[89] The choice between these agents depends on individual response and adverse effects.[9]

If an appropriate dose of a single agent does not adequately control symptoms, consider combining a ß-agonist with a muscarinic antagonist.[9] Albuterol in combination with ipratropium is available in a single metered dose inhaler (Combivent). The **COMBIVENT** trial found that combination therapy with albuterol and ipratropium provided better bronchodilation in patients with COPD than either agent alone, without increasing adverse effects.[90]

Long-acting inhaled bronchodilators

Long-acting inhaled bronchodilators for COPD include long-acting ß-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs). There are now several types of LABAS—salmeterol (Serevent Diskus), formoterol (Foradil Aerolizer, Perforomist), arformoterol (Brovana), indacaterol (Arcapta), and olodaterol (Striverdi)—and several types of LAMAs—tiotropium (Spiriva), aclidinium (Tudorza), umeclidinium (Incruse), glycopyrronium (Seebri), glycopyrrolate (Lonhala Magnair), and revefenacin (Yupelri). 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.[9] Most studies of inhaled corticosteroid (ICS) monotherapy show no benefits in terms of either FEV_1 or

mortality.[91] 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 (see sections below on GOLD guidelines for initial therapy and GOLD guidelines for adjusting medications).

Combination maintenance inhalers

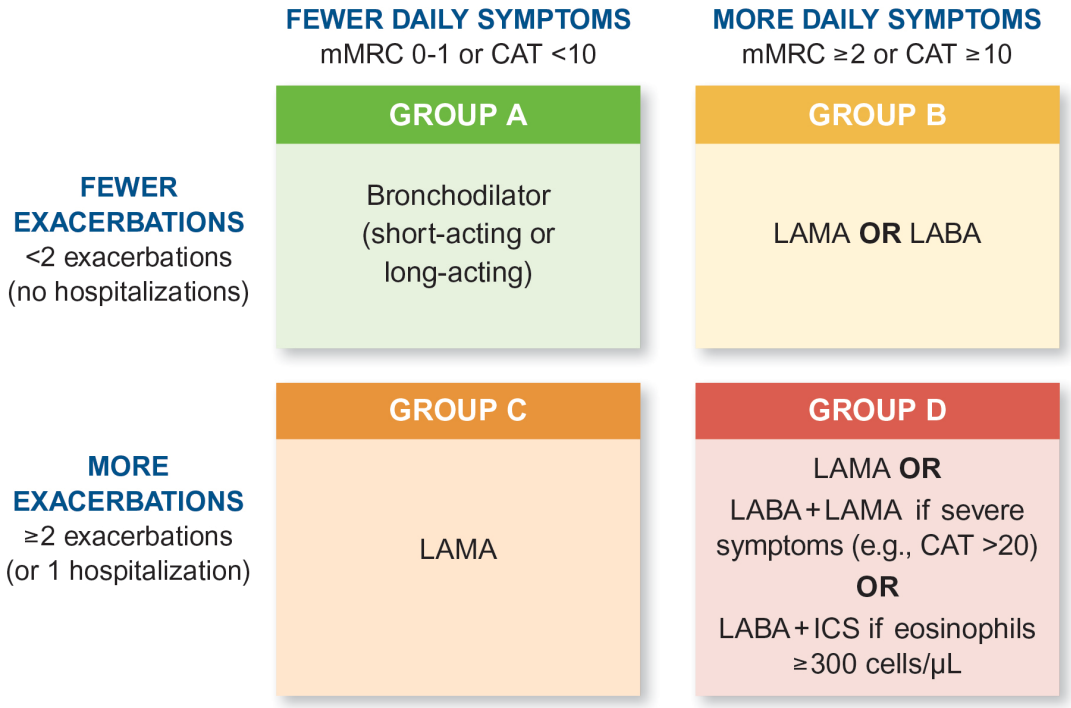
There are currently 3 categories of maintenance inhalers that combine the ingredients (LABA, LAMA, and/or ICS) discussed above:

- **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 Diskus, Advair HFA, AirDuo, Wixela); fluticasone/vilanterol (Breo)
- **ICS + LAMA + LABA:** fluticasone/umeclidinium/vilanterol (Trelegy); budesonide, glycopyrrolate/formoterol (Breztri Aerosphere)

GOLD guidelines for initial therapy

The 2020 GOLD guidelines specify that GOLD groups should be used to guide initial therapy when treating a patient with COPD but that decisions about medication adjustment should be made based on separate algorithms for dyspnea and exacerbations (see below).[9] These separate algorithms for medication adjustment are new in the 2020 GOLD guidelines. All initial treatment decisions for patients with COPD confirmed on spirometry should be made according to Figure 6.

Figure 6: Daily symptom severity and history of exacerbations in the prior year are used to group patients and guide treatment selection.[9]



LABA: long-acting beta agonist; **LAMA:** long-acting muscarinic antagonist; **ICS:** inhaled corticosteroid

DAILY SYMPTOMS:
Defined according to either the mMRC scale, which focuses on dyspnea (scores from 0-4), or the COPD Assessment Test [CAT]), which includes dyspnea and other symptoms (scores from 0-40). See **AlosaHealth.org/COPD** for assessments.

EXACERBATIONS:
Discrete episodes characterized by acute worsening of symptoms (i.e., increased dyspnea, sputum volume, purulence) beyond usual day-to-day variation and requiring intervention.

GOLD guidelines for adjusting therapy

The 2020 GOLD guidelines provide two different algorithms to use when adjusting therapy. The choice of algorithm will depend upon whether the patient needs escalation of therapy due to worsening dyspnea or more exacerbations. The two algorithms are provided in Figures 7 and 8 (next page).

Figure 7: GOLD algorithm for dyspnea

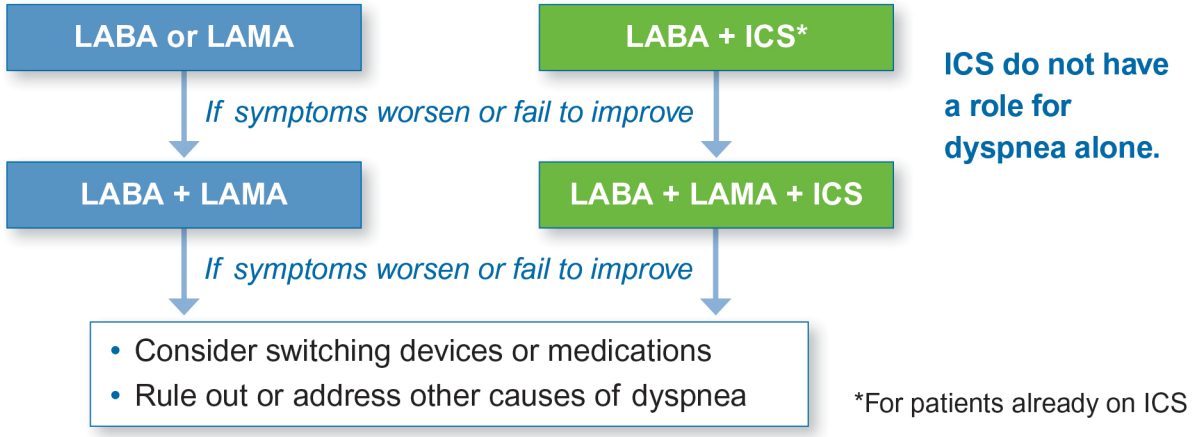
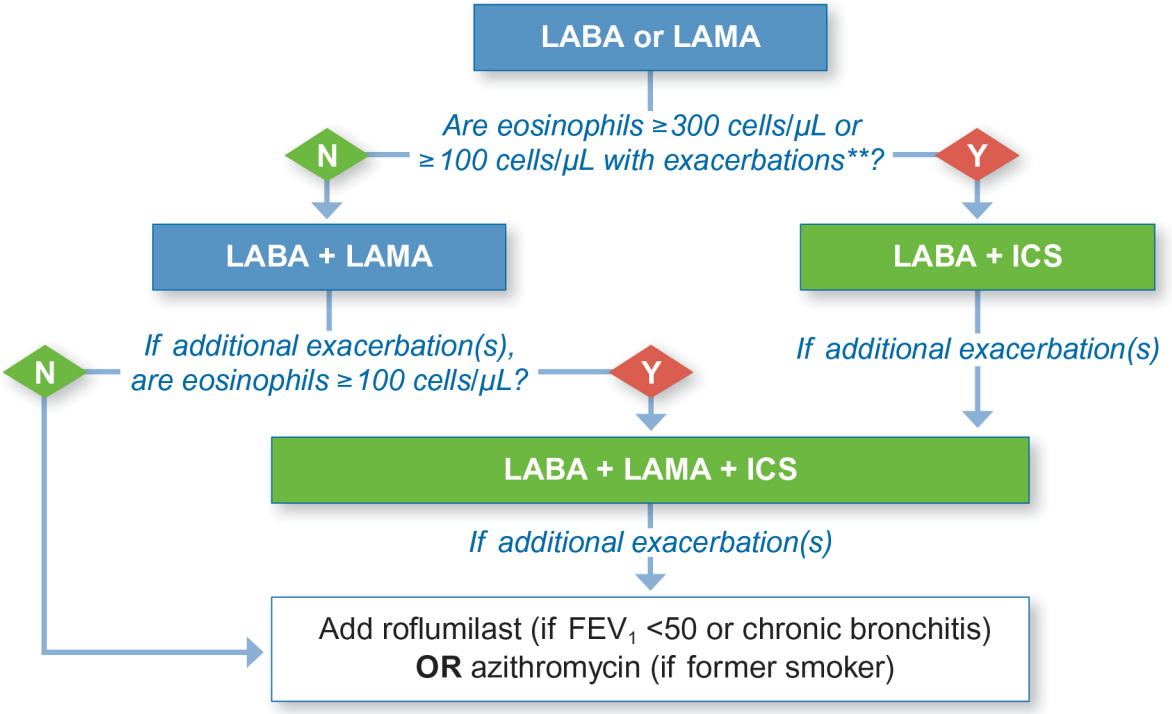


Figure 8: GOLD algorithm for exacerbations



**2 moderate exacerbations or 1 exacerbation requiring hospitalization

The GOLD guidelines (both for initial therapy and adjustment of therapy) reserve inhaled corticosteroids for only a specific subset of COPD patients. The algorithms provide specific cutoffs regarding the number of exacerbations and/or the peripheral eosinophil counts that may drive decisions to start inhaled corticosteroids. More general considerations are summarized in Table 3. 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 3: Factors to consider when initiating ICS treatment[9]

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

Evidence underpinning use of inhalers in COPD

Rationale for starting LAMA or LABA monotherapy in early COPD

Three large long-term studies have 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.[92]

While lung function (pre- and post-bronchodilator) was significantly better 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; p<0.001). There were no significant differences between the groups in hospitalization rates.

The **TORCH** study examined the effect of salmeterol/fluticasone propionate combination therapy and its individual components on the survival of COPD patients.[93] **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

Trial duration was 3 years and the primary endpoint was all-cause mortality. Secondary endpoints were rate of exacerbations and health-related quality of life.[93] Table 4 summarizes results comparing the LABA salmeterol with placebo.

Table 4: TORCH results, salmeterol vs. placebo[93]

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; p<0.001)
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 salmeterol vs. placebo

The TORCH trial also demonstrated the superiority of ICS-LABA therapy over LABA monotherapy in preventing COPD exacerbations and improving health status and spirometry. While consensus has emerged that combination therapy may be beneficial for some patients with COPD who do not respond to monotherapy, the optimal first-line combination therapy (whether ICS plus LABA or LAMA plus LABA) remains debated. This question has been explored in several further trials after the TORCH trial (the details of which are provided in the next section).

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.[94] 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.

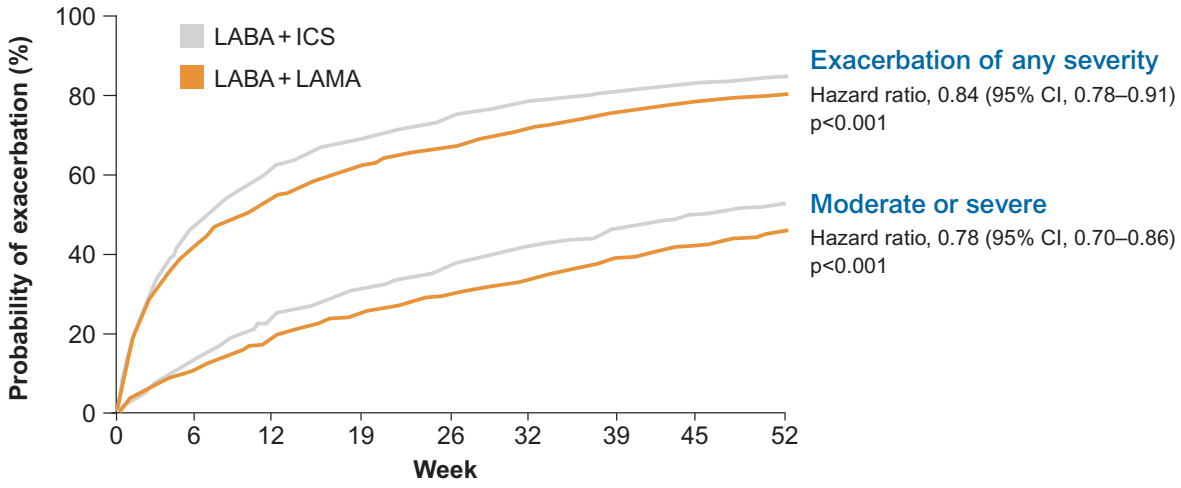
Rationale for stepping up therapy with more advanced COPD

LABA + LAMA combination therapy

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.[95] There was also a reduction in exacerbations with tiotropium added to a LABA, and insufficient evidence to determine risks and benefits of the different LABAs.[95]

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 an FEV_1 of 25-60% predicted for 52-weeks to either indacaterol with glycopyrronium or salmeterol with fluticasone.[96] The LABA/LAMA combination resulted in a 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 9: Probability of exacerbation in the FLAME trial[96]



Combination therapy with an ICS

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:[97]

- triple therapy with the ICS fluticasone furoate (100 mcg), the LAMA umeclindinium (62.5 mcg), and the LABA vilanterol (25 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 triple therapy (i.e., Trelegy) 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 higher incidence of pneumonia in the inhaled-glucocorticoid groups than in the umeclidinium/vilanterol group.

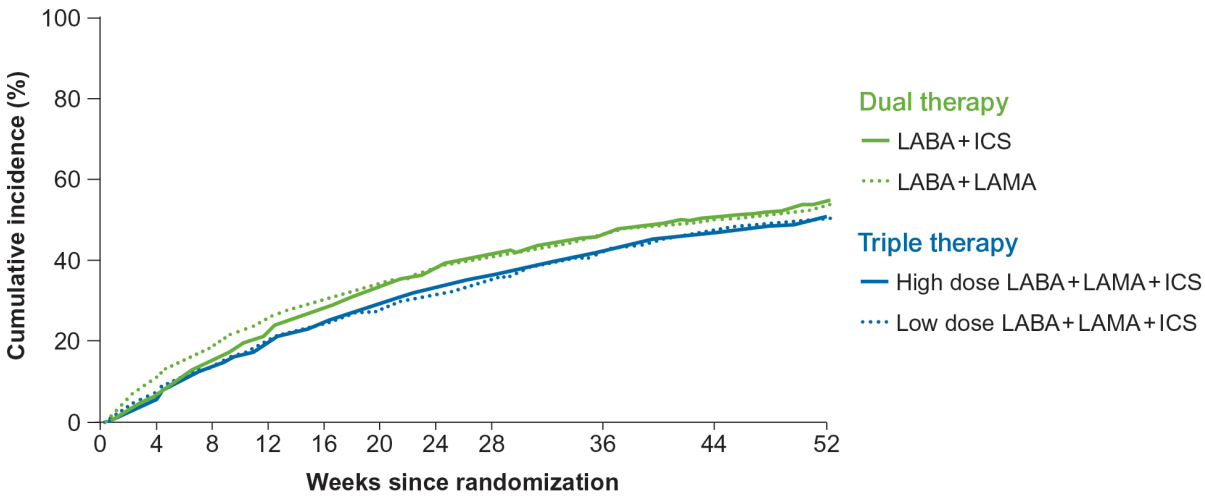
An important limitation of the IMPACT trial is that patients with asthma, who are more likely to benefit from inhaled corticosteroids, were included.[98] Another criticism is that many patients were on inhaled corticosteroids at baseline prior to randomization—nearly 40% on triple therapy and 70% on inhaled corticosteroids.[99] When these patients were randomized to the LAMA/LABA group, their inhaled corticosteroids were abruptly withdrawn, which could have predisposed them to exacerbations.[99] 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).[98] 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 dose levels of inhaled glucocorticoid in 8,509 patients with moderate-to-very-severe COPD and at least one exacerbation in the past year.[100] 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 320 mcg budesonide, 18 mcg glycopyrrolate, and 9.6 mcg formoterol
- triple therapy with 160 mcg of budesonide, 18 mcg glycopyrrolate, and 9.6 mcg formoterol
- dual therapy with 18 mcg of glycopyrrolate plus 9.6 mcg of formoterol
- dual therapy with 320 mcg of budesonide plus 9.6 mcg of formoterol

The primary end point (annual rate of moderate or severe exacerbations) was significantly lower with 320 mcg budesonide 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 10: Time to first moderate or severe exacerbation in ETHOS[100]



Withdrawal of inhaled corticosteroids

Inhaled corticosteroids, alone or in combination, are associated with higher rates of oral candidiasis, hoarse voice, skin bruising, and pneumonia.[91] 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 **WISDOM** (Withdrawal of Inhaled Steroids during Optimized Bronchodilator Management) trial 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.[101] 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.[101]

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).[102] 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 did, however, lead to a statistically significant reduction in mean FEV_1 of -26 ml (95% confidence interval, -53 to 1 ml) at 182 days.

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 non-physician health professionals such as nurses or 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 adherence to inhaler procedures in only 23% of patients.[103] The elderly are particularly vulnerable to this problem because many have 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 such as the Turbuhaler and Accuhaler require a greater inspiratory flow to deliver medication to the lower airways than pressurized metered and soft mist inhalers, which can result in inadequate delivery particularly in older patients, women, and those with short stature or decreased forced vital capacity.[56]

Many patients benefit from using a metered dose inhaler (MDI) with a spacer, especially if severe disease is present. 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 [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 in some, but not all, patients.[104] 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.[105] In addition, review inhaler use at the time of any exacerbation.

A detailed description of how to use various forms of inhalers (MDI, spacers, Turbuhaler, Accuhaler, Respimat, etc.) can be found at AlosaHealth.org/COPD. 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.[106-109]

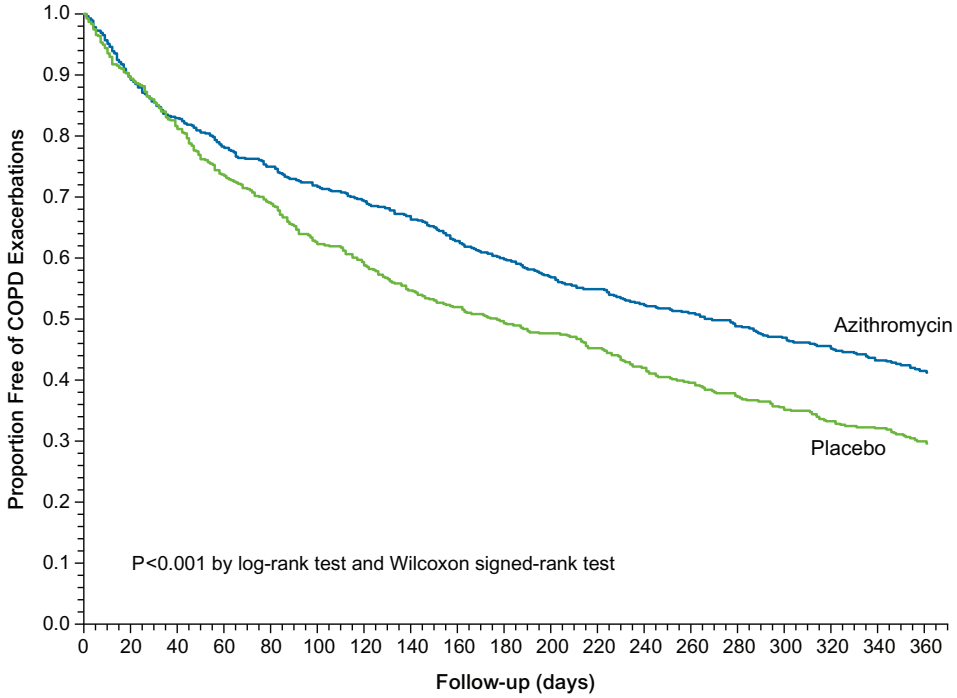
BOTTOM LINE: Evidence to guide the choice of an initial long acting bronchodilator is not conclusive. The data suggest a slight reduction of exacerbations with LAMAs versus LABAs, though there is substantial heterogeneity in the findings of individual studies. Some patients on LAMA or LABA monotherapy will require a step-up to combination inhaler therapy in order to control symptoms. The FLAME trial showed that patients randomized to LAMA + LABA combination therapy had fewer exacerbations and pneumonias than patients randomized to ICS + LABA combination therapy. For most patients who require a step-up in therapy, the recommendation from GOLD is therefore to use LAMA + LABA inhalers as the first-line combination therapy. However, patients with frequent exacerbations and high eosinophil counts may particularly benefit from the addition of an ICS, whether as the initial combination therapy (ICS + LABA) or as part of a triple therapy regimen (ICS + LAMA + LABA). Thus, GOLD recommends ICS use for a specific subset of COPD patients. Data continue to emerge about which patients are more likely to benefit from one inhaler therapy versus another. Optimal therapy with any inhaled medication relies on both adherence and good inhaler technique.

Evidence for other medications in COPD

Macrolide antibiotics

The use of antibiotics in patients with stable COPD has been controversial, but some relatively recent studies have shed light on this issue. A trial that administered three months of oral clarithromycin in stable COPD found no improvement in health status, sputum bacteriology, or exacerbation rates in patients treated with antibiotic compared to placebo.[110] However, 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.[111] Patients treated with erythromycin had shorter duration exacerbations compared with placebo. There were no differences in FEV_1 between the antibiotic and placebo groups.[111]

Figure 11: Patients without acute COPD exacerbation on azithromycin vs. placebo[112]



Proportion of participants free from acute exacerbations of Chronic Obstructive Pulmonary Disease (COPD) 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.[112] 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%) (Figure 11). This effect was additive to other therapies for COPD, since >80% of patients were on 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 rate of death between placebo and azithromycin.

Possible concerns regarding long-term macrolide therapy include hearing loss, potentially fatal QTc prolongation, and the development of antibiotic resistance.[113,114] 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 are known to raise the risk of QTc prolongation.[115,112,116]

Phosphodiesterase-4 inhibitors

Phosphodiesterase-4 (PDE_4) inhibitors are a newer class of drugs with some clinical efficacy in the management of moderate-to-severe COPD. The principle action of PDE4 inhibitors is to reduce

inflammation by inhibiting the breakdown of intracellular cyclic AMP.[117] Inhibitors of the PDE_4 isoenzyme have anti-inflammatory and bronchodilatory properties in the lungs.[118] Two PDE_4 inhibitors have been extensively studied: cilomilast and roflumilast (Daliresp). Currently only roflumilast is FDA approved for reducing COPD exacerbations (once-daily oral medication). PDE_4 inhibitors have more adverse effects than inhaled medications for COPD, the most common being diarrhea, nausea, reduced appetite, weight loss, sleep disturbances, and headache.[119]

A 2017 Cochrane Review identified 34 published and unpublished placebo-controlled trials on roflumilast (n=17,627) and a second PDE_4 inhibitor cilomilast that is not FDA approved (n=6,457) in patients with a wide range of disease severities.[120] The meta-analyses showed that the PDE_4 inhibitors reduced the risk for exacerbations vs. placebo (overall OR 0.78; 95% CI: 0.73-0.83), improved mean FEV_1 (mean difference 51 mL; 95% CI: 43-60 mL), but resulted in no significant change in exercise tolerance.

Both drugs produced diarrhea, nausea, abdominal pain, headache, and unexplained weight loss that led to withdrawal from treatment; they are contraindicated in moderate to severe liver disease. While most of these studies were compared to placebo, 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.[121] The rate of moderate-to-severe exacerbations was 13% lower in the treatment group (0.81 vs. 0.93), though with higher withdrawal in the roflumilast group. Given the minimal improvements in measures other than exacerbations, PDE_4 inhibitors are generally recommended as an adjunct to other treatments.

Mucolytics

A 2019 Cochrane review (38 trials, n=10,377) found that in adults with stable chronic bronchitis or COPD, regular treatment with oral mucolytics, usually n-acetylcysteine (NAC), was associated with an increased likelihood of being exacerbation-free during the study period compared to placebo (OR 1.73; 95% CI: 1.56-1.91) although more recent studies show less benefit than was reported in earlier studies.[122] The Chinese **PANTHEON** trial found that NAC 600mg twice daily reduced the risk of exacerbations (RR 0.78 after one year).[123] However, issues such as a high dropout rate and inclusion of never smokers and subjects on other therapies (~50% on ICS/LABA, ~10% on LAMA) may limit its applicability to other COPD cohorts. Some data suggest that benefit occurs more during winter, and in patients not already on inhaled steroids. For example, the **BRONCUS** (Bronchitis randomized on NAC) study of 523 patients with COPD did not find a significant reduction in exacerbations with n-acetylcysteine at 600 mg daily compared to placebo, although a significant reduction was seen in the subgroup of patients not being treated with ICS.[124]

Other drug treatments

Agents such as leukotriene receptor antagonists, cromoglycate, and nedocromil, often used in asthma, have not been adequately studied in COPD and cannot be recommended.

Managing exacerbations

Exacerbations present challenges to COPD patients and their clinicians, and require strategies beyond maintenance therapy.[9] They can occur in any stage of COPD but are more common in moderate or severe disease.[125,126]

Exacerbations cause:[9]

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

Symptoms typically include some combination of worsening dyspnea, cough, increasing volume or purulence of sputum, and chest congestion, accompanied by further impairment of lung function and gas exchange. A severe exacerbation can lead to life-threatening respiratory failure and an extended recovery period.[127]

Between 3% and 16% of exacerbations require hospitalization,[19,128] and in severe episodes, mortality can be as high as 10%.[33] Up to 25% of patients who require admission to an intensive care unit will die.[126] The prevention and treatment of exacerbations is thus a major objective of COPD management.[9]

Etiology

The main causes of COPD exacerbations include:[9]

- bacterial infections (*Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, *Enterobacteriaceae*, and *Pseudomonas aeruginosa*); *Pseudomonas aeruginosa* and *Staphylococcus aureus* are more common in severe COPD than in less severe disease
- viral infections (rhinoviruses, influenza, parainfluenza, respiratory syncytial virus, adenovirus, and coronavirus)
- 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.[9] 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.[19,129,130]

Diagnosis

Early diagnosis and prompt management of exacerbations may prevent progressive functional deterioration and reduce hospital admissions.[9] The presenting symptom of increased dyspnea may be accompanied by increased cough and sputum production, wheezing, chest tightness, change of sputum

color. Non-specific symptoms such as fever, malaise, insomnia, sleepiness, fatigue, depression, and confusion may occur.

The assessment of an exacerbation is based on functional status before the exacerbation, symptoms, and potentially arterial blood gas measurements and a chest X-ray. Acute changes in test results are more clinically relevant than absolute values. In patients with severe COPD, a change in mental alertness signals a need for immediate evaluation.[9]

An increase in sputum purulence (i.e., color) may suggest a bacterial cause.[131] 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.[127] Exacerbations may also result from the acquisition of new strains of existing bacteria. Sputum cultures are not routinely performed nor recommended in primary care.

Differential diagnoses for worsening symptoms in a patient with stable COPD include:[9]

- pneumonia
- pneumothorax
- pleural effusion
- pulmonary embolus
- pulmonary edema due to cardiac related conditions
- coronary artery disease
- arrhythmia

Hospitalization

Hospitalization may be necessary if any of the following are present:[9]

- marked increase in intensity of symptoms, such as sudden onset of resting dyspnea
- increasing use of accessory muscles of respiration
- severe background COPD or frequent exacerbations
- presence of high-risk co-morbidities such as pneumonia, cardiac arrhythmia, heart failure, diabetes mellitus, renal or liver failure
- older age
- onset or worsening of physical signs (e.g., cyanosis, peripheral edema)
- acute confusion or other change in mental state
- failure of exacerbation to respond to initial medical management
- inability to manage symptoms safely at home

Bronchodilators

First-line management for dyspnea in an exacerbation should begin with a short acting ß-agonist (albuterol), and/or a short acting anticholinergic (ipratropium), which can be given by MDI and spacer, or by nebulizer. Administering bronchodilators with a nebulizer has no clear advantage over an MDI at equivalent doses in patients able to correctly use these devices.[108]

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 initiation after resolution of the exacerbation.

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.[9]

A 2014 Cochrane review found that short-term treatment of exacerbations with oral or parenteral corticosteroids:[132]

- 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

A long course of systemic glucocorticoids (up to 14 days) was considered standard in the past. However, the **REDUCE** trial comparing 40 mg prednisone daily for 5 vs. 14 days in patients who presented to the emergency department with an acute COPD exacerbation found that 5-day treatment was non-inferior in terms of repeat exacerbations and time to a next exacerbation.[133] A 2018 Cochrane review including this study and others concluded that five days is sufficient.[134] In general, prednisone 40 mg/day for 5 days is recommended as there is no advantage in prolonged therapy.[9] 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.[9] Such use confers a substantial risk of osteoporosis, cataract development, hyperglycemia, and other serious adverse effects.[127] In an outpatient setting, inhaled corticosteroids (ICS) should be continued during an exacerbation, and, if not previously used, should be considered in order to reduce the risk of further exacerbations.[9,133]

Antibiotics

Efficacy

Many patients with acute COPD exacerbations are treated with antibiotics, but the value of antibiotics is relatively modest and uncertain, 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.[135] 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). Evidence from one trial in outpatients suggested no effects of antibiotics on mortality.[135] Only one trial (n=35) reported health-related quality of life but did not show a statistically significant difference between treatment and control groups.[135]

Evidence of moderate quality from the Cochrane review does not show that currently-used antibiotics reduce the risk of treatment failure among inpatients with severe exacerbations (i.e. for inpatients excluding ICU patients). Evidence of moderate quality from two trials including inpatients shows no beneficial effects of antibiotics on mortality.[135] One trial with 93 patients admitted to the ICU showed a

large and statistically significant effect on treatment failure (RR 0.19; 95% CI: 0.08-0.45 and a significant effect on mortality (OR 0.21; 95% CI: 0.06-0.72).

Who will benefit

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.[9] New evidence suggests that C-reactive protein (CRP) may have a role to play in guiding antibiotic prescribing during COPD exacerbations.[136]

Choice of agent

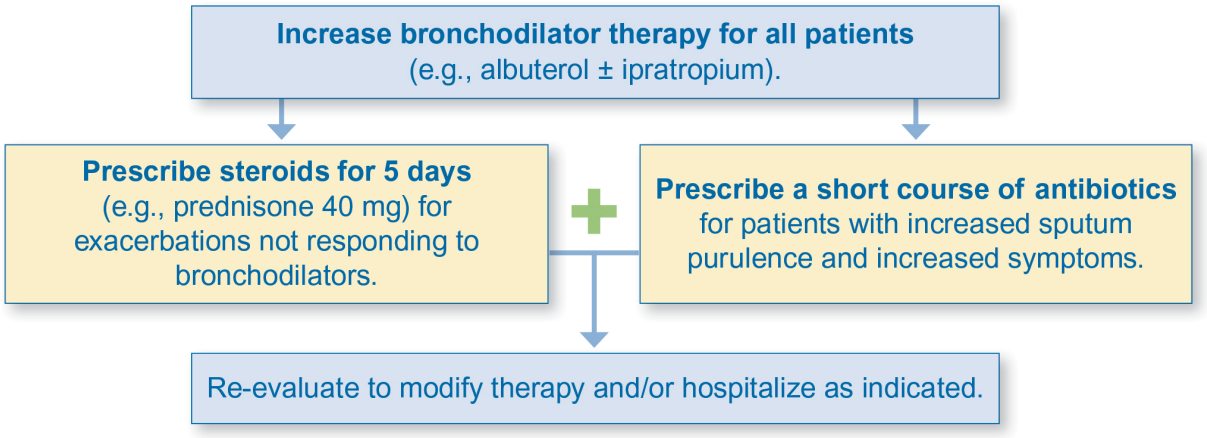
Appropriate antibiotic prescribing is based on the pathogens that are most common in COPD exacerbations and is guided by any previous sputum cultures and/or local resistance patterns.[9] Since bacterial colonization is common in patients with COPD, sputum cultures during exacerbations are not clinically 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).[56]

Duration of therapy

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.[137] Most of the studies included in the meta-analysis were conducted in the community.[137]

Putting it all together: Managing exacerbations

Figure 12: Managing a COPD exacerbation in the outpatient setting[9]



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 and usually requires use of short-term bronchodilators. Oral prednisone and antibiotics may also be appropriate in selected patients.

Non-pharmacological interventions for COPD

Immunization

A 2018 Cochrane review of two trials with 180 patients with either COPD or other chronic lung diseases found that inactivated influenza vaccination reduced the frequency of exacerbations vs. placebo (mean difference -0.37 exacerbations per vaccinated participant).[138] Annual vaccination against influenza is recommended in the 2020 GOLD report.[9]

The 23-valent pneumococcal polysaccharide (PPSV23 or Pneumovax) vaccination is recommended for patients with chronic lung disease, including COPD, once before the age of 65.[139] It is also recommended for all adults after age 65, including re-administration for patients with chronic lung disease who received the vaccine before the age of 65.

The 13-valent conjugate vaccine (PCV13 or Prevnar) is no longer routinely recommended for adult patients with COPD.[140] The reason is that the strains covered by PCV13 have become increasingly rare with the success of childhood pneumococcal vaccines (and associated herd immunity).[141] The current recommendation from the Centers for Disease Control and Prevention is for clinicians and patients to engage in shared clinical decision-making about PCV13. If the decision is made to pursue vaccination with PCV13, then the patient should receive PCV13 once at age 65 followed by PPSV23 one year later. However, if the patient has already received PPSV23 after age 65 (but before a decision is made about PCV13), PCV13 can still be given so long as it is given one year after PPSV23.

The Centers for Disease Control and Prevention does not provide substantial guidance yet about how to engage in shared decision-making with patients. Shah et al. suggest clarifying that the vaccine is safe and effective at the individual-level but is no longer routinely recommended to everyone because its benefits at the population-level are low.[142] The following conditions were proposed as examples that might lead to a recommendation in favor of PCV13 for individual patients:[142]

- Chronic medical conditions: chronic heart, liver, or lung disease, DM, aspiration, dysphagia, esophageal motility disorders, IBD
- Group living: nursing homes, assisted living, jails, shelters, homeless
- Prior pneumonias
- Residing in areas with low rates of childhood PCV13 immunization
- Substance use: alcohol, smoking, crack cocaine, opioids
- Use of medications that may increase pneumonia risk: proton-pump inhibitors, antipsychotics, opioids, sedatives

Exercise

All COPD patients can benefit from exercise training programs, which may improve muscle strength, exercise tolerance, dyspnea, and fatigue.[143] A 2016 meta-analysis of 37 RCTs involving 4,314 patients with COPD found that exercise training alone, or with the addition of activity counseling, significantly improved physical activity levels.[144] A relatively small (n=47) observational study found that a combination of constant load or interval training with strength training resulted in better outcomes for COPD patients than either method alone.[145]

Endurance exercise of the leg muscles is the main focus of exercise training, whether formal or informal, with walking, stationary cycling, and treadmill exercises. Encourage patients to engage in endurance exercises to 60-80% of their symptom-limited maximum work or heart rate, although lower intensity exercise is also beneficial.[9] A resistance exercise component for the legs and arms may help in some activities of daily living. Exercise training can be enhanced by optimizing bronchodilator therapy before exercise sessions.[9]

Nutrition

Weight loss and muscle wasting occur in 20-35% of patients with stable COPD, and can contribute to increased mortality and morbidity.[34] 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). This can include small frequent meals with energy-rich supplements in quantities divided during 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 (Megace, Megestrol) may increase body weight, but the weight gain often consists of fat mass only, so such appetite stimulants are not recommended.[34,146] Combine nutritional support with exercise wherever possible.[34] Referral to a nutritionist may be helpful if a patient is unable to maintain a healthy weight.

Self-management education

Select patients who are at risk of COPD exacerbations and who can reliably self-manage, should be encouraged to:[147]

- Increase their bronchodilator therapy as appropriate to control symptoms
- Start an oral corticosteroid if increased breathlessness interferes with activities of daily living
- Begin antibiotic therapy

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). 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.[147] No significant mortality benefit was observed, however. Of note, one randomized controlled trial of a

comprehensive care management program vs. usual care was terminated early due to unexpectedly high mortality in the intervention group (28 deaths vs. 10 deaths, p=0.003) and a non-significantly higher rate of COPD-related hospitalizations (27% vs. 24%) after a mean follow-up of 250 days).[148]

Pulmonary rehabilitation

Introduction

Pulmonary rehabilitation is a supervised exercise and strength training program during which patients can also get education about their disease or symptoms. Pulmonary rehabilitation does not directly improve lung function, but has been shown to be the most effective therapeutic strategy to improve shortness of breath, health status, and exercise tolerance.[149] Pulmonary rehabilitation programs can also reduce anxiety and depression, reduce the frequency of exacerbations and hospitalization, and possibly reduce mortality.[9]

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.[150]

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 so common in patients with COPD.[9] Home-based rehabilitation can be as effective as outpatient, hospital-based rehabilitation.[151] (The essential elements of such programs are presented below.) 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.[152]

Patient selection

Current GOLD guidelines recommend pulmonary rehabilitation for all COPD patients with GOLD Group B, C, or D disease.[9] Pulmonary rehabilitation is not recommended for patients with unstable cardiac disease.[146]

Pre-initiation testing and duration

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.[153]

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.[9]

Maintenance

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.[9]

Availability

Formal pulmonary rehabilitation programs are not available to many patients who could benefit from this approach. 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.

The 2015 American Thoracic Society/European Respiratory Society policy statement on pulmonary rehabilitation provides practical information on exercise, body composition/nutrition, self-management, psychological and social issues, and outcomes assessment.[154] (Available at: thoracic.org/statements/resources/copd/implem-pulm-rehab.pdf)

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),[155] though it may not improve survival in patients with less severe hypoxemia or in those with only nocturnal oxygen desaturations.[156]

Long-term oxygen should be started in patients with stable disease on a full medical regimen if they have:[157]

- 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 if:

- PaO_2 ≥60 mmHg with exercise desaturation, sleep desaturation not corrected by continuous positive airway pressure (CPAP), or severe dyspnea responding to O_2

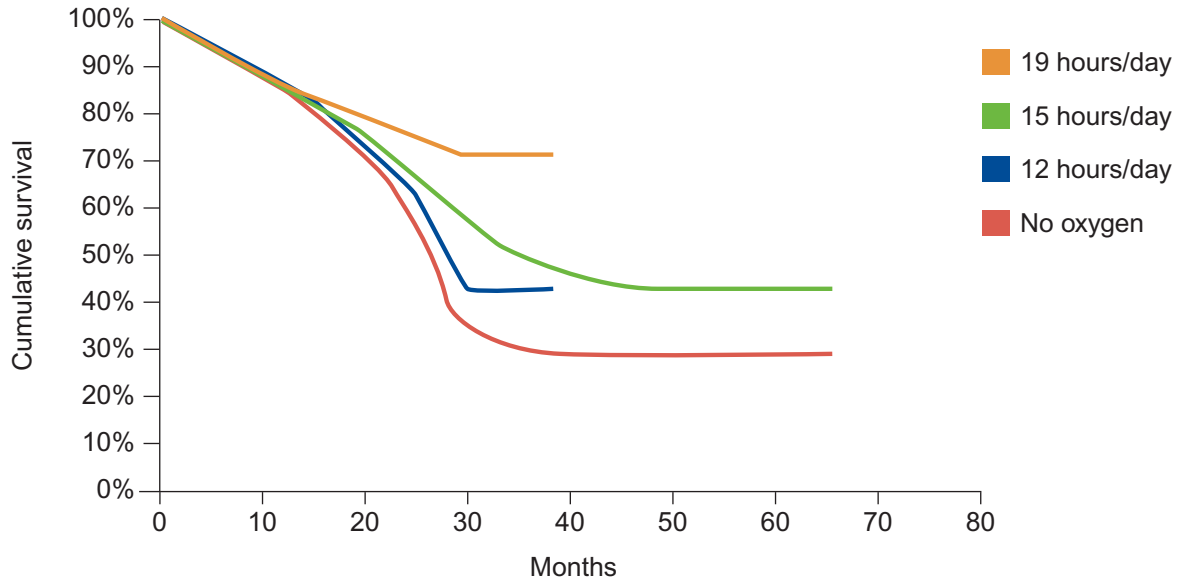
When titrating oxygen, the goal is to maintain SaO_2 >88%-90% during rest, sleep, and exercise.[34]

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.[156] 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.

However, whether some patients with mild hypoxemia may still benefit from supplemental oxygen is unclear. A Cochrane review found that patients with COPD can exercise longer and have less shortness

of breath when using oxygen during exercise,[158] while a 2019 trial found no differences in exercise capacity or quality of life in 111 patients randomized to oxygen supplementation vs. room air.[159]

Figure 13: Trials of long-term oxygen therapy[160,32]



Noninvasive Ventilation

A study of noninvasive ventilation with oxygen therapy 2-4 weeks after hospitalization found that patients with persistent hypercapnea ($PaCO_2$ >53 mm Hg) or hypoxemia (PaO_2 <55 mm Hg or <60 mm Hg with additional factors) 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).[161] 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.[162] Two studies from 2014 with approximately 200 patients each were not included in the Cochrane review and reported conflicting results.[163,164] Many trials did not assess for undiagnosed sleep apnea, which, when treated, improves survival and the risk of hospitalization.[9] The 2020 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.[9] 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.[9]

BOTTOM LINE: Immunize for influenza annually and pneumococcus before age 65 and after, encourage exercise and adequate nutrition, and provide self-management education in all patients

with COPD. Refer patients with more symptoms or a history of exacerbation to pulmonary rehabilitation. In patients with chronic hypoxemia, prescribe home oxygen therapy.

Advanced disease

Referral for surgical or bronchoscopic lung volume reduction

Surgical options for severe COPD are limited and pose some risks, but may be appropriate for selected patients.[10] Lung volume reduction involves the removal of damaged tissue from one or both upper lobes, which may allow the remaining lung sections to expand and 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.[165]

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.[166]

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 (about 5 years) remains far below that associated with the transplantation of other solid organs.[167]

End-of-life considerations

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 the need for ventilatory support. Does the patient prefer aggressive management such as hospitalization or mechanical ventilation, or comfort-focused interventions? Failure to address these issues proactively when the patient is stable often results in much avoidable 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 end-of-life care, including the appointment of a health care proxy. Discussions should prepare patients for a life-threatening exacerbation, and address their decisions regarding life support by providing information on probable outcomes of each treatment option. Patients may choose to refuse life supportive care or have it withdrawn. 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.[9]

A literature review of palliative and end-of-life care 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:[168]

- 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

Below are some suggestions for talking about end-of-life care, prognosis, and advance care planning.[168]

Initiating discussions

- Frame the discussion as an important part of care for all patients with severe COPD.
- Identify whether the patient is able to make his or her own medical decisions.
- Ask whether a family member or other person should be present for the discussion.

Discussing prognosis

- Ask if the patient is willing to discuss prognosis; if so, deliver prognosis and confirm understanding.
- Use numeric or visual expressions of risk rather than qualitative statements.
- Frame prognosis as referring to groups of people rather than individuals.
- Explicitly acknowledge uncertainty in prognostication, since acute exacerbations events are difficult to predict.

Discussing advance care planning

- Frame as ‘‘hope for the best and prepare for the worst.’’
- If appropriate, clarify that advance care planning with a clinician does not diminish a clinician’s focus on maximizing the patient’s survival.
- Discuss the importance of advance directives if patients have strong views about the use of cardiopulmonary resuscitation, mechanical ventilation, or other treatments.
- Discuss the importance of advance directives if patients have a preference for another person to make medical decisions for them, especially if that preference does not match the default surrogate decision-maker according to local laws.
- Identify whether there are specific health states that the patient would consider ‘‘worse than death.’’
- Explicitly discuss a commitment to non-abandonment.
- Offer patients the opportunity to talk about their spirituality or religion.

Palliative care should be available to patients at different stages of COPD and individualized to the needs and preferences of the patient and family.[169] 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.[34]

Patients with COPD may qualify for formal hospice services, which can provide excellent support and symptom control. Many episodes of worsening dyspnea in patients coming to the end of life can be avoided with appropriate hospice care.

Further information on palliative care for patients with chronic respiratory disease, including practical approaches to the management of dyspnea, pain, and the psychological challenges related to suffering and dying, is available from the American Thoracic Society. For links to this and other information, visit AlosaHealth.org/COPD.

Palliative treatment of refractory dyspnea

Breathlessness is a common cause of suffering in people with advanced and terminal disease and should be assessed routinely.[170] Low-dose opioids should be considered for patients with end-stage COPD and refractory dyspnea. 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), and after an initial response, further dose increases should not occur for at least one week.[171] 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.[170]

Systemic effects of COPD and co-morbid conditions

Cardiovascular disease

Hypertension is the most common concurrent disease among patients with COPD,[172] and both COPD and cardiovascular disease are characterized by systemic inflammation, which may play a role in the pathogenesis of both diseases.[173] Smoking is a significant causal factor in both COPD and cardiovascular disease. The management of hypertension in most patients with COPD is similar to that of the general population, with consideration of the pulmonary effects of antihypertensive therapies, which may vary by drug class. A review of contemporary evidence supports the use of ACE inhibitors, ARBs, and thiazides in patients with COPD after consideration of the risks of adverse effects and interactions with medications used for management of COPD.[174]

Sleep apnea

Obstructive sleep apnea occurs in about a third of COPD patients and contributes to fatigue and decreased function.[175] Evaluate excessive daytime sleepiness or sleep-disordered breathing in all COPD patients, especially those with obesity. This may require consideration of sleep studies, weight loss, reduced alcohol intake, and nocturnal CPAP.

Gastro-Esophageal Reflux Disease (GERD)

GERD is a risk factor for COPD exacerbations.[176] Lifestyle changes, including smoking cessation, reduced intake of caffeine and alcohol, weight loss, exercise, and elevation of the head of the bed may help GERD symptoms.[176] A therapeutic trial of an H_2-receptor antagonist or proton-pump inhibitor may help clarify this diagnosis.

Osteoporosis

Patients with COPD often have below-normal bone mineral density (BMD) and an increased risk of fractures, because of smoking, use of corticosteroids, and decreased weight-bearing activity. Inhaled corticosteroid therapy has been associated with fractures in some pharmaco-epidemiological studies, though the recommendation is still to use inhaled corticosteroids in COPD (if needed) even among patients with osteoporosis.[9] The association between systemic corticosteroids and osteoporosis is strong, and efforts should be made to avoid use of oral or intravenous steroids for long-periods or frequently for exacerbations.

Aspiration

Educate at-risk patients about the hazards of aspiration and the importance of safe swallowing techniques, including avoiding talking when eating, sitting upright, taking small mouthfuls of food and drink, chewing thoroughly, taking liquids with dry foods, using a straw, and drinking thickened fluids.

Pulmonary hypertension and heart failure (*cor pulmonale*)

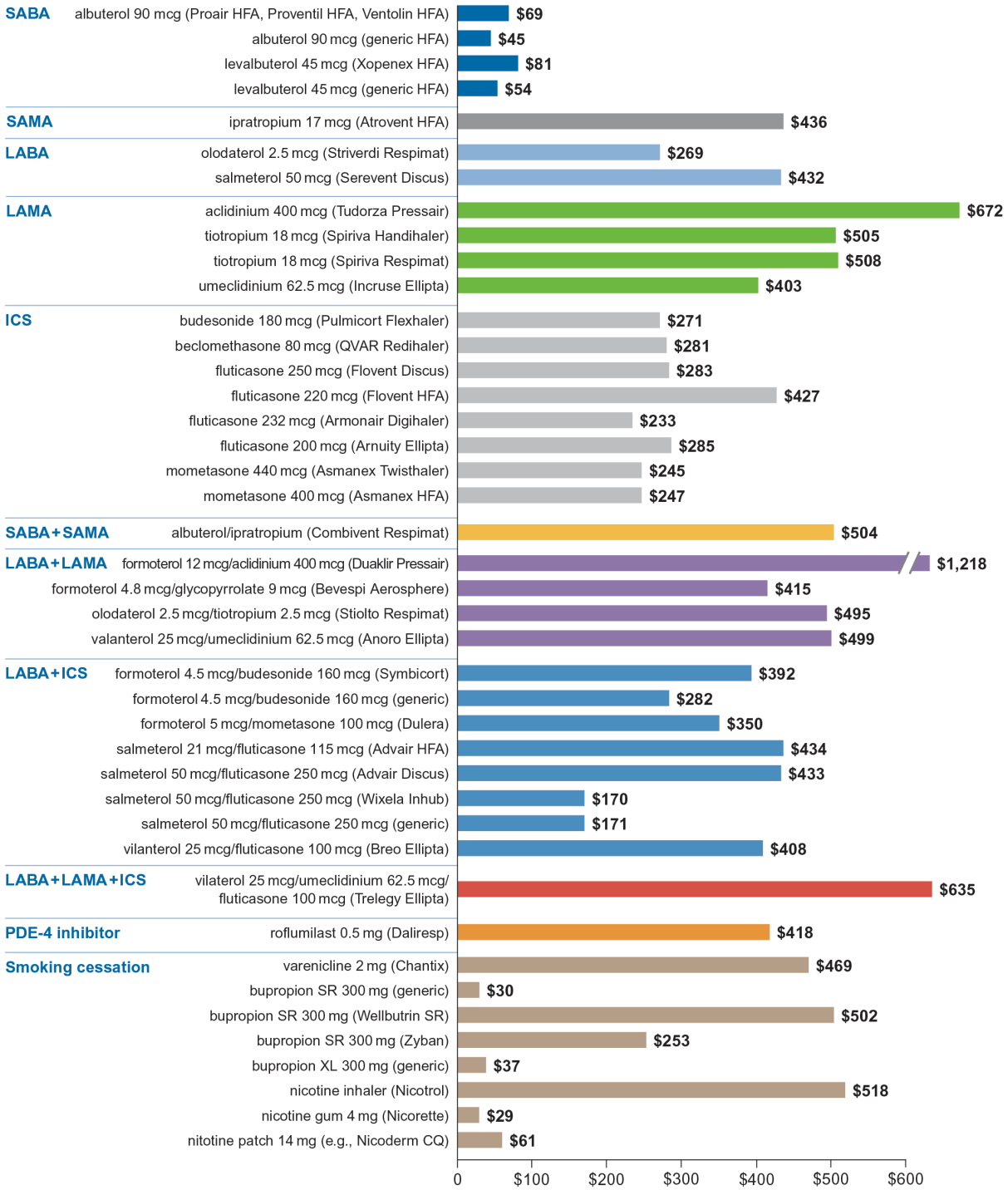
Chronic hypoxia can lead to pulmonary hypertension, which can cause right heart failure (*cor pulmonale*). The treatment of pulmonary hypertension that occurs secondary to chronic lung disease differs from the treatment of primary pulmonary hypertension or pulmonary hypertension that occurs secondary to cardiac disease. Oxygen therapy and diuretics may be beneficial, but data are mixed for targeted therapies, including prostacyclin pathway agonists, phosphodiesterase inhibitors, and endothelin receptor antagonists.[177]

Anxiety and depression

Anxiety and depression are common in COPD and should be assessed and treated.[20,178] These conditions may be exacerbated by medications such as theophylline and systemic steroids.

Costs of COPD Medications

These are the 30-day costs of the defined daily dose for each agent or combination product. A list of medications used in COPD is provided in Appendix 1.



Prices from goodrx.com, May 2020. Listed doses are based on Defined Daily Doses by the World Health Organization and should not be used for dosing in all patients. All doses shown are for generics when available, unless otherwise noted. These prices are a guide; patient costs will be subject to copays, rebates, and other incentives.

Not all inhalers are FDA approved to treat COPD.

Appendix 1: COPD medications

Category	Type	Formulations	Brand names
Inhaled short-acting β-agonists (SABA)	Albuterol (also known as salbutamol)	MDI DPI Nebulized solution	ProAir HFA Proventil HFA Ventolin HFA ProAir Digihaler ProAir Respiclick Accuneb
	Levalbuterol	MDI Nebulized solution	Xopenex Xopenex HFA
Inhaled long-acting β-agonists (LABA)	Arformoterol	Nebulized solution	Brovana
	Formoterol (also known as eformoterol)	DPI Nebulized solution	Foradil Perforomist
	Olodaterol	Soft mist inhaler	Striverdi Respimat
	Salmeterol	DPI	Serevent
Inhaled short-acting anticholinergics (SAMA)	Ipratropium	MDI Nebulized solution	Atrovent HFA Generics
Inhaled long-acting anticholinergics (LAMA)	Aclidinium	DPI	Tudorza Pressair
	Revefenacin	Nebulized solution	Yupelri
	Glycopyrrolate	Nebulized	Lonhala Magnair
	Glycopyrronium	Dry powder inhaler	Seebri
	Tiotropium	MDI DPI	Spiriva Spiriva Respimat
	Umeclidinium	DPI	Incruse Ellipta
Inhaled combination products SABA/SAMA	Albuterol/Ipratropium	MDI Nebulized solution	Combivent DuoNeb
Inhaled combination products **LAMA / LABA**	Formoterol/Aclidinium	DPI	Duaklir Pressair
	Formoterol/Glycopyrrolate	MDI	Bevespi Aerosphere

Category	Type	Formulations	Brand names
	Olodaterol/Tiotropium	MDI	Stiolto Respimat
	Vilanterol/Umeclidinium	DPI	Anoro Ellipta
Inhaled combination products **LABA / ICS**	Formoterol/Budesonide	MDI	Symbicort
	Formoterol/Mometasone	MDI	Dulera*
	Salmeterol/Fluticasone	MDI DPI	Advair HFA Advair Diskus Airduo Respiclick Airduo Digihaler Wixela Inhub
	Vilanterol/Fluticasone	DPI	Breo Ellipta
Triple combination **LABA / LAMA / ICS**	Formotorol/Glycopyrrolate/Budesonide	MDI	Breztri Aerosphere
	Vilanterol/Umeclidinium/Fluticasone	DPI	Trelegy Ellipta
Phosphodiesterase-4 inhibitors	Roflumilast	Tablet	Daliresp

* not FDA approved for the treatment of COPD

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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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