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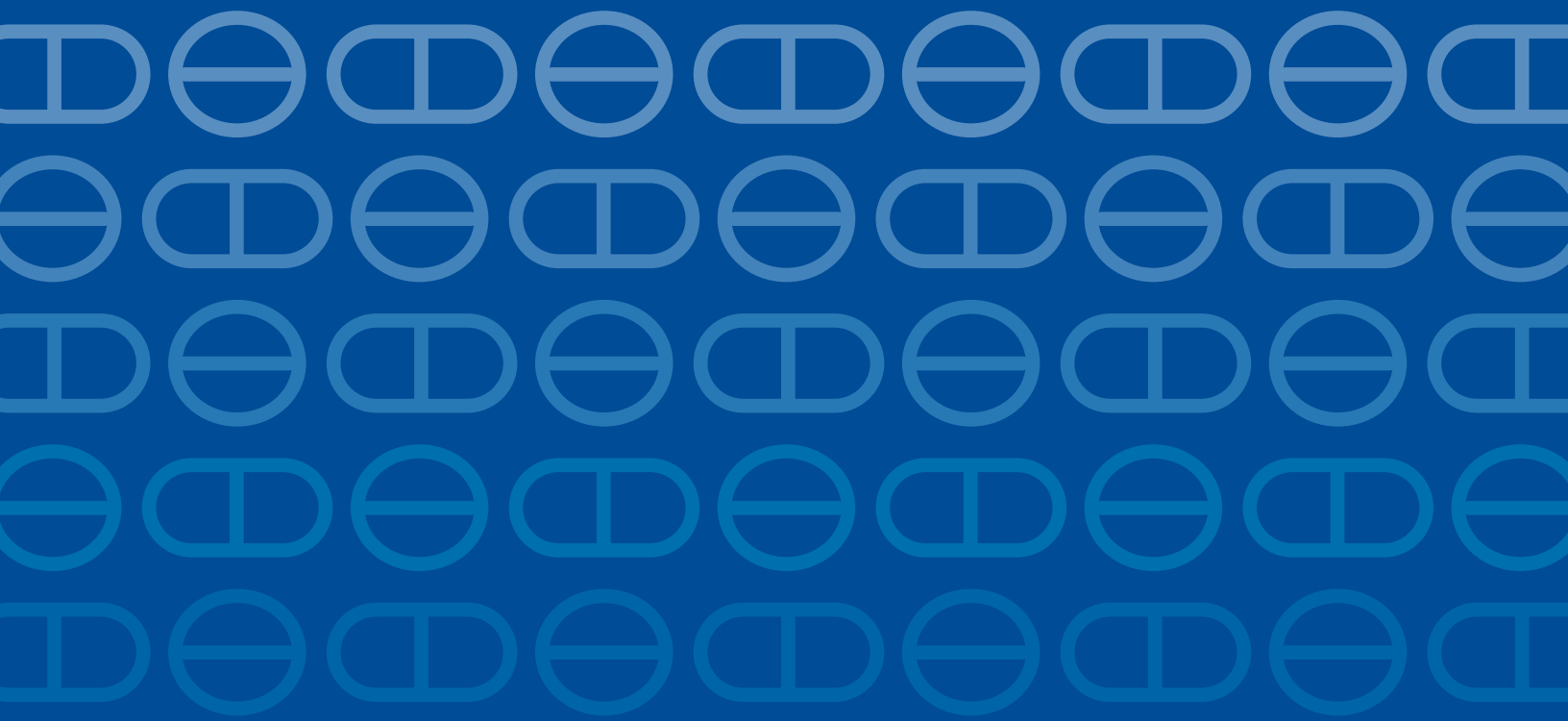
Helping patients with COPD breathe easier

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



Helping patients with COPD breathe easier

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

Principal Consultant: Michael H. Cho, M.D., M.P.H.

Series Editors: Michael Fischer, M.D., M.S. (principal editor), Jerry Avorn, M.D., Niteesh K. Choudhry, M.D., Ph.D., Dae Kim, M.D., Sc.D., Ellen Dancel, PharmD., M.P.H.

Medical Writer: Stephen Braun

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Helping patients with COPD breathe easier

Accreditation:

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education 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.

Credit Designation:

The Harvard Medical School designates this enduring material for a maximum of 1.50 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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 in physicians’ offices 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 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 diagnose COPD
- Classify patients according to the GOLD system based on symptoms and history of exacerbations.
- For patients who smoke, begin by assessing their willingness to quit, and then tailor recommendations appropriate for their stage of readiness.
- Prescribe a regimen of exercise, good nutrition, and immunizations for all patients with COPD.
- Match drug therapy to disease severity, symptoms, and risk of exacerbation according to the GOLD system.
- Prescribe oxygen for patients with chronic hypoxemia.

- Treat acute exacerbations aggressively with short-acting bronchodilators, systemic steroids, and antibiotics where appropriate.

Disclosure Policy:

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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.

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Faculty and Planners:

Michael H. Cho, M.D., M.P.H. is an Assistant Professor in the Division of Pulmonary and Critical Care Medicine and the Division of Network Medicine at Brigham and Women’s Hospital Medicine and Harvard Medical School. Dr. Cho has received research grant support from GlaxoSmithKline.

Michael Fischer, M.D., M.S. is an Associate Professor of Medicine at Harvard Medical School and a primary care internist who studies cost-effective drug use in outpatient practices. Dr. Fischer has no relevant financial relationships to disclose.

Dae Kim, M.D., Sc.D., is an Assistant Professor of Medicine, Harvard Medical School and a geriatrician and epidemiologist at Brigham and Women’s Hospital. Dr. Kim has no relevant financial relationships to disclose.

Jerry Avorn, M.D. is a Professor of Medicine at Harvard Medical School and Chief of the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham and Women's Hospital. An internist, he has worked as a primary care physician and geriatrician and has been studying drug use and its outcomes for over 30 years. Dr. Avorn has no relevant financial relationships to disclose.

Niteesh K. Choudhry, M.D., Ph.D. is a Professor of Medicine at Harvard Medical School and a hospitalist at Brigham and Women's Hospital. His research focuses on the use of medications to treat common chronic conditions. Dr. Choudhry has no relevant financial relationships to disclose.

Ellen Dancel, Pharm.D., M.P.H., is the Director of Clinical Materials Development at Alosa Health. Dr. Dancel has no relevant financial relationships to disclose.

Stephen Braun, B.A. is a medical writer based in Amherst, MA. Mr. Braun has no relevant financial relationships to disclose.

Reviewers:

Carolyn E. Come, M.D., M.P.H. is an Instructor in Medicine at Harvard Medical School and a pulmonary and critical care physician at Brigham and Women's Hospital. Her primary research interests are exploring the association between COPD and cardiovascular disease and the impact of lung volume reduction on cardiopulmonary physiology. Dr. Come has no relevant financial relationships to disclose.

Susan O'Brien is a CME Reviewer for Harvard Medical School Global and Continuing Education. Her role is to review CME proposals for compliance with regulatory requirements. Ms. O'Brien has no relevant financial relationships to disclose.

Media used:

Printed educational material.

Instructions for Participation and Credit:

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Email: cme@alosahealth.org

Mailing address:

Alosa Health
419 Boylston Street, 6th Floor
Boston, MA 02116

Fax: 857-350-9155

The activity will take approximately 1.50 hours to complete.

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

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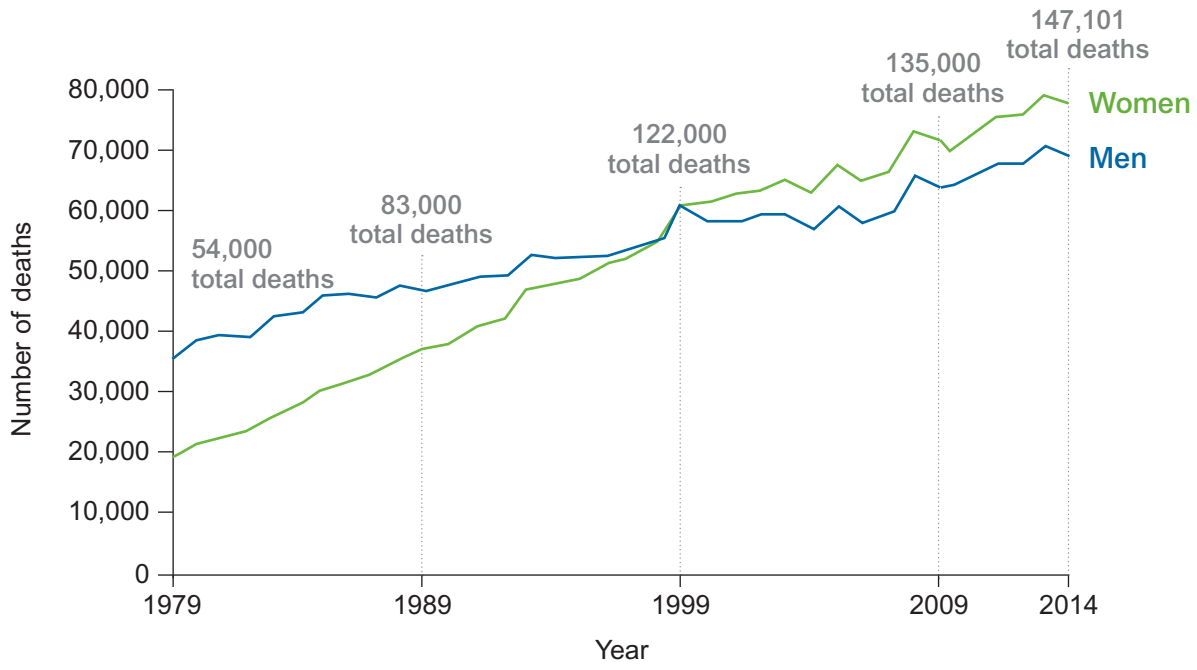
The burden of COPD

Chronic obstructive pulmonary disease (COPD) is a significant national and global public health problem. It is the third-leading cause of death in the US, behind cancer and heart disease.[1] For the past decade, more women have died of COPD each year than men, a reversal of earlier trends (Figure 1), which is attributable in large part to the increase in smoking among women.[1] Roughly 15 million Americans have been diagnosed with COPD, although the actual prevalence is likely much higher because more than half of adults with reduced pulmonary function are not aware of their condition until they are diagnosed by a physician.[2,3] By 2020 the total costs attributable to COPD are estimated to reach $49 billion in the US.[4] Between 50% and 75% of such costs result from exacerbations of the disease.[5]

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[6,7]



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 an enhanced inflammatory response to noxious environmental stimuli.[8] It is characterized by dyspnea on exertion and, often, extra-pulmonary effects.[9]

Previous definitions of COPD emphasized emphysema and chronic bronchitis. 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. 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 absence of airflow obstruction, and vice versa. In fact, narrowing and disappearance of small airways appears in pathologic studies to precede the development of emphysema and be the major contributor to obstruction.[10]

Asthma is a chronic inflammatory disease of the airways characterized by variable and recurring symptoms, and 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.[8] These differences in the inflammatory process 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.[11] In addition to inflammation, a protease/anti-protease imbalance exists in the lungs of COPD patients, 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:[11]

- 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”), and which is a major cause of dyspnea in patients with severe disease[12,13]
- destruction of alveoli, which impairs gas exchange and leads to hypoxemia and hypercapnia
- hypoxic vasoconstriction of pulmonary arterioles, causing pulmonary hypertension[14]

Many COPD patients have some airflow limitation that can be ameliorated by bronchodilators, and some patients with chronic asthma develop irreversible airway narrowing. It is therefore often not 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.[15] The co-occurrence of asthma and COPD (or the asthma COPD overlap syndrome, ACOS) has been increasingly recognized. Recently, the Global Initiative for Asthma (GINA) and GOLD collaborated to develop guidelines for ACOS.[16]

Natural history

The course of COPD can be highly variable. 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.[17,18] Among COPD patients, some have relatively stable lung function, and others have more rapid decline.[19] Exacerbations generally lead to deterioration in lung function,[20] worsening morbidity, more frequent hospitalizations, and

reduction in quality of life.[9,21] Progressive airflow limitation may lead to disability and early death, and differs from the reversible airway obstruction of asthma.[16]

Risk factors for developing COPD

Factors contributing to the development of COPD include:[8,22]

- smoking
- occupational dust and fume exposure
- outdoor air pollution[23]
- exposure to biomass (e.g., wood, dung, straw) smoke from fires for cooking or heating[24]
- genetic factors, most notably Alpha1-anti-trypsin deficiency
- recurrent severe respiratory infections in childhood
- maternal smoking
- asthma

Smoking is by far the most common contributing cause of COPD in industrialized countries, although exposure to biomass smoke may be the biggest risk factor globally.[5,22,25,26] 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 tobacco smoke damage.

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.[5,11,27,28] In susceptible smokers, cigarette smoking results in a steady decline in lung function, with a decrease in FEV_1 of 25–100 mL/year. About 20% of COPD is attributable to occupational dust and fumes.[5,8] Urban/outdoor air pollution likely only accounts for a small percentage of COPD, although it may be a significant trigger for exacerbations.[23]

Systemic effects

COPD patients frequently have significant comorbidities, particularly those with advanced disease.[8] Barnett et al., found that 82% of COPD patients had two or more additional conditions.[29] Westney, et al., analyzed patterns of COPD comorbidities in 291,978 adult COPD patients in a nationally representative Medicaid claims data set.[30] 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%).[30]

Other common COPD comorbidities include:

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

- ischemic cardiovascular disease
- pulmonary hypertension and right-sided heart failure (*cor pulmonale*)
- 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 about 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.[31]

Hyperinflation: the degree of hyperinflation as measured by inspiratory capacity/total lung capacity (IC/TLC) ratio independently predicts all-cause and COPD mortality.[32]

Respiratory failure: the development of hypoxemic respiratory failure (partial pressure of arterial oxygen [PaO2]/fraction of inspired oxygen [FiO2] <300] or respiratory rate >24)[33] is an independent predictor of mortality, with a three-year survival rate of about 40%.[34]

Hypercapnia: patients with partial pressure of arterial CO_2 ($PaCO_2$) >50 mmHg have a mortality rate of 11% during hospital admission and 49% at 2 years.[35] The 5-year survival rate for those with chronic CO_2 retention (about 25% of those admitted with hypercapnic exacerbations) is only 11%.[35]

Body mass index (low and high), **degree of dyspnea,** and **frequency of acute exacerbations** also predict mortality and should be evaluated in all patients.[5]

BODE and e-BODE indices: BODE (body mass index, airflow obstruction, dyspnea and exercise capacity) and e-BODE (BODE plus exacerbations) predict 6-month mortality.[36,37]

Emphysema: Increased emphysema, as measured by computed tomography, is a risk factor for mortality.[38,39]

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

Diagnosis

COPD is substantially under-diagnosed and can occur at an earlier age than is generally suspected.[22] Early 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.[11,40] Such early detection and aggressive treatment can alter the natural history of the disease.

Medical history

When assessing a patient for COPD, the medical history should include:[5,8]

- 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, allergy, 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 exacerbation or previous hospitalizations for respiratory disorder (these may not have been defined or identified as exacerbations of COPD)
- 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[8]

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 may show dilated heart or pulmonary edema • Pulmonary function tests indicate 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 in 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

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 wheeze, 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 of 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 and can sometimes be performed in the office or can be done rapidly in a pulmonary function testing laboratory (available in most hospitals or medical facilities). Patients can have moderately impaired lung function before they develop 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 two most commonly assessed functional values on spirometry are:

- **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 which the patient can forcibly exhale after taking the deepest breath possible.

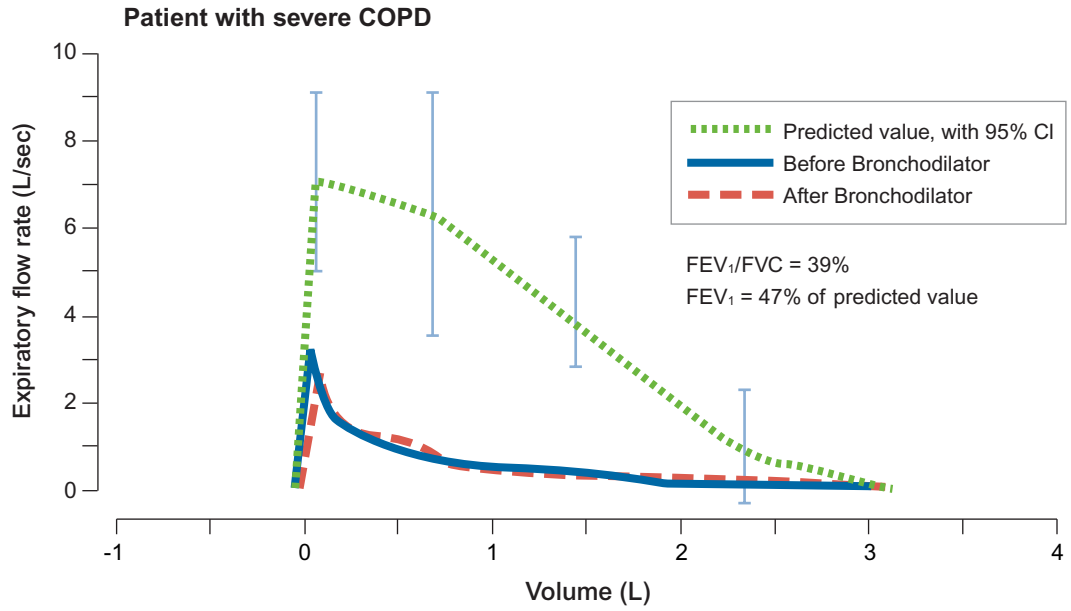
A post-bronchodilator $FEV_1/FVC < 0.70$ in the appropriate clinical setting confirms the diagnosis of COPD.[8] The FEV_1/FVC ratio tends to decline with age, and thus has been criticized for potentially under-diagnosing younger and over-diagnosing older patients. However, GOLD advocates the use of this fixed ratio due to simplicity of interpretation and independence of the measure from reference values. The GOLD grades of obstruction (all with $FEV_1/FVC < 0.7$) are as follows:

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

- Very Severe; FEV_1 <30% predicted

Note that these grades of obstruction based on spirometry are not the same as the A, B, C, D groups in the 2017 GOLD guidelines—the stages based on spirometry are now used as just one component of a diagnostic scheme that incorporates symptoms and exacerbation history, which are detailed below. Figure 2 presents spirometry findings found in severe COPD.

Figure 2: Spirometry in COPD[46]



Adapted from: The COPD-X Plan; available at: *http://copdx.org.au/guidelines/index.asp*

While GOLD is the most commonly-used set of guidelines, an alternative is the COPD foundation system. This system also has specific treatment recommendations for severity of obstruction and symptoms, and uses five spirometric grades.[47] These grades reflect many clinical trials that included subjects with FEV_1 <60% predicted, and formally classify subjects with impaired spirometry but without obstructive physiology.

- **Spirometry Grade (SG) 0**—Normal spirometry; does not rule out emphysema, chronic bronchitis, asthma, or risk of developing either exacerbations or COPD.
- **SG 1 Mild**—Post bronchodilator FEV_1/FVC ratio <0.7, FEV_1>60% predicted.
- **SG 2 Moderate**—Post bronchodilator FEV_1/FVC ratio <0.7, 30%< FEV_1 <60% predicted.
- **SG 3 Severe**—Post bronchodilator FEV_1/FVC ratio <0.7, FEV_1 <30% predicted.
- **SG U Undefined**— FEV_1/FVC ratio >0.7, FEV_1 <80% predicted (no obstruction present, but a decrease in FEV_1). This is consistent with restriction, muscle weakness, and other pathologies.

Quantifying respiratory symptoms

Although quantification of airflow obstruction is very useful for the diagnosis of COPD, other factors will guide treatment decisions. Symptoms including dyspnea, cough, sputum, exercise capacity, and the frequency of acute 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.[48]

A similar, but even shorter, tool is the modified Medical Research Council (mMRC) dyspnea scale (Table 2).[8,49]

Table 2: mMRC dyspnea scale

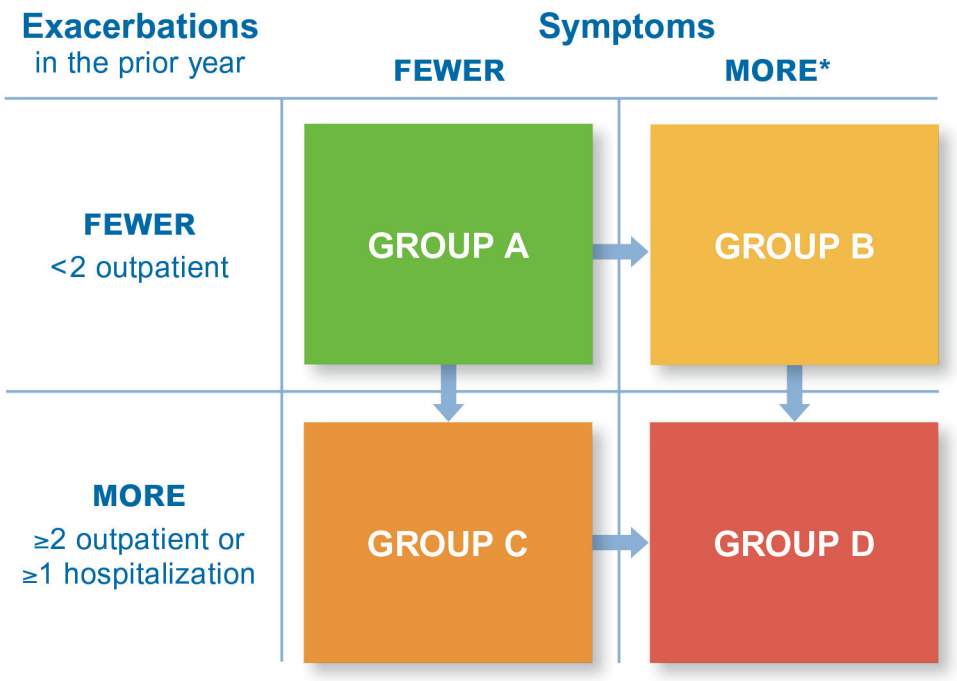
Grade	Description of breathlessness
0	I only get breathless with strenuous exercise
1	I get short of breath when hurrying on level ground or walking up a slight hill
2	On level ground, I walk slower than people of the same age because of breathlessness, or have to stop for breath when walking at my own 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 used as one of 3 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 COPD Guidelines, though the CAT may be superior as it assesses symptoms other than just breathlessness.

COPD Staging: The GOLD Criteria

The 2017 GOLD criteria were updated to use airflow obstruction as measured by spirometry only for diagnosis and prognosis, and to use symptoms (dyspnea and cough) and the frequency of acute exacerbations to guide treatment decisions[8] The criteria are formulated based on groups determined by both risk and symptom severity (Table 3).

Table 3: The GOLD classification system[8]



Additional Assessment Tools

Chest Imaging

A chest X-ray is rarely diagnostic for COPD unless obvious bullous disease of emphysema is present, but can be useful in identifying or excluding other conditions such as pneumonia, heart failure, lung cancer, pleural effusions, tuberculosis, and pneumothorax.[50] Similar considerations apply for chest CT scans, though many COPD subjects may meet criteria for screening CT scans for lung cancer due to smoking history.

Alpha-1 antitrypsin deficiency

Alpha-1 antitrypsin deficiency 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. A serum value of alpha-1 antitrypsin <15–20% of the normal value is highly suggestive of homozygous alpha-1 antitrypsin deficiency.[8]

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, clinical symptoms, and history of exacerbations to

diagnose COPD and classify patients using the GOLD 4-group system, which will guide treatment decisions.

Managing stable COPD

Goals and principles of management

Aggressive treatment can alter the natural history of the disease, and non-pharmacologic approaches can be surprisingly beneficial.[40] The goals of COPD management include:[8]

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

Managing COPD may involve:

- smoking cessation
- non-drug therapies
  - immunization
  - exercise
  - good nutrition
  - pulmonary rehabilitation
  - supplemental oxygen
  - surgery (lung volume reduction surgery, lung transplantation)
- medications
  - inhaled bronchodilators
  - inhaled corticosteroids
  - medications for smoking cessation
  - phosphodiesterase 4 inhibitors
  - chronic azithromycin
  - methylxanthines
  - oral steroids and antibiotics for exacerbations

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.[8]

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 as shown by spirometry.[8] 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.

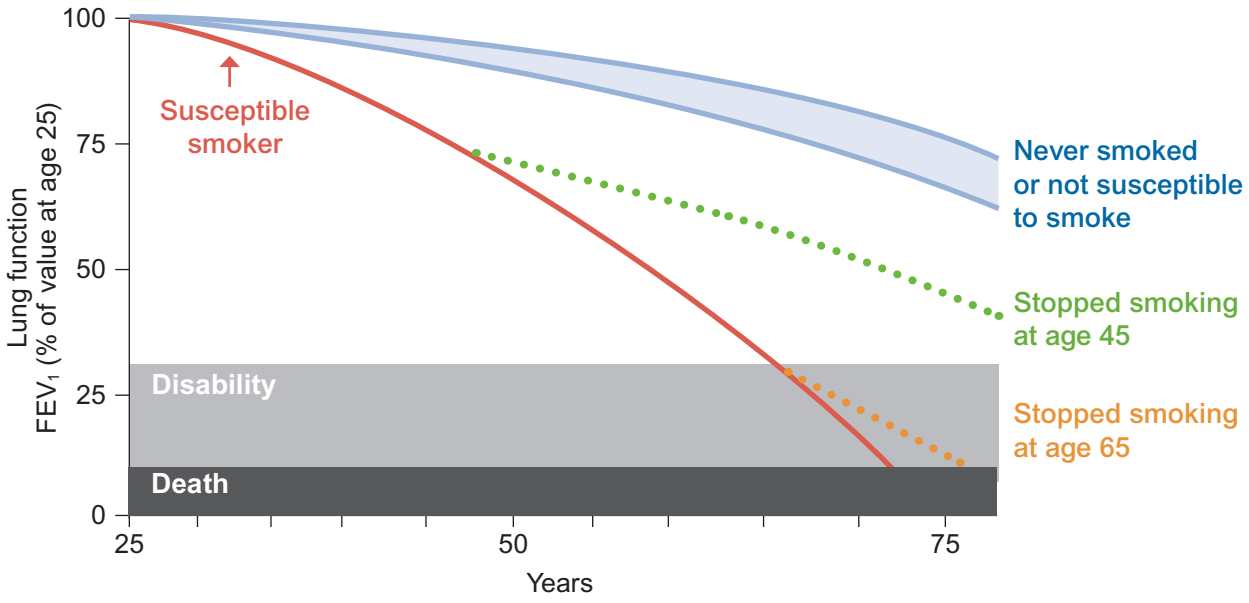
Spirometry should be performed whenever a significant worsening of symptoms or a major complication occurs. Spirometry in stable disease can provide useful information on the rate of decline in lung function, although it is unnecessary as part of routine visits for patients with stable COPD.[8]

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.[11,22,51,52] A 2008 systematic review found that stopping smoking slows the rate of lung function decline and improves survival, even in patients with severe COPD.[53] Smoking cessation also reduces the risk of exacerbations, with the magnitude of the reduction dependent upon the duration of abstinence.[54]

Figure 3 (next page) 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 quitting cigarettes.

Figure 3: Smoking and decline of lung function in COPD[55]



Smoking cessation is thus a key intervention in all stages of COPD.[22,52,56-58] 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":

- *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:

- 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:

- Relevance: point out the effects of smoking on their *own* health: e.g., if they had an MI, 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. A successful tobacco cessation program might include the following:[59]

- 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 an outlet for anxiety while quitting, such as an exercise program
- Screen for psychiatric disease: smoking is more common in patients with depression, schizophrenia, and alcohol abuse; often smoking cessation will not be successful 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 may be found at AlosaHealth.org/COPD

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.[60] 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%.[59] While there are no clear counseling components critical to a successful program, the number of sessions is important, with the greatest impact seen with 4 sessions of at least 10 minutes in length.[59] Phone follow-up by a non-MD provider is very useful.[62]

Medications to help with quitting

Good evidence suggests that the following pharmacotherapies can be effective to support smoking cessation, unless contraindications are present:[63]

- nicotine replacement therapy (gum, lozenges, transdermal patches, inhaled, 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)

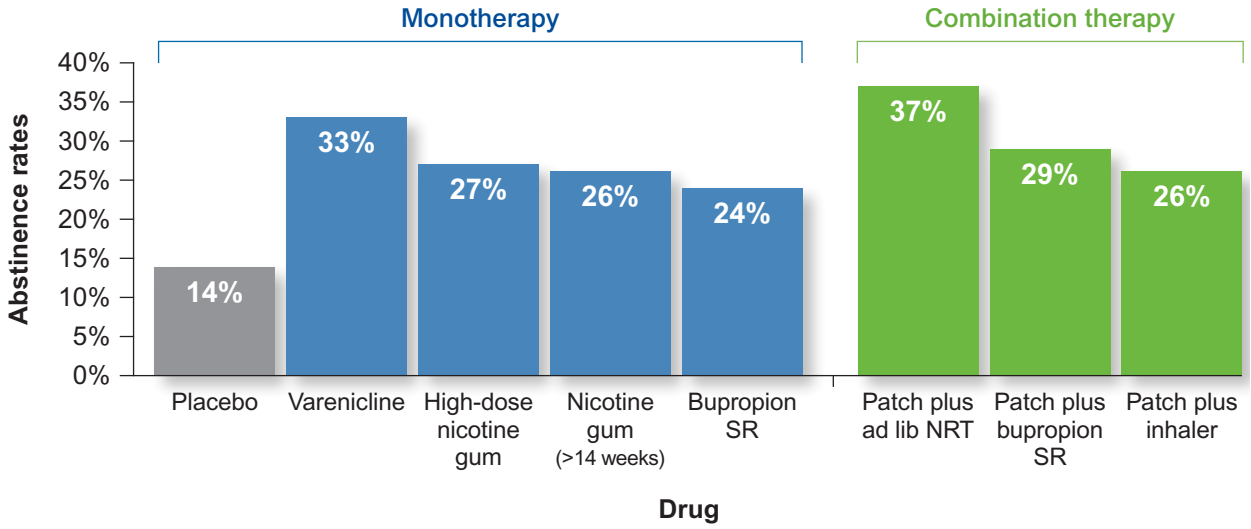
Varenicline (Chantix) was found to be marginally superior to bupropion (Zyban, Wellbutrin, others) in some studies and in a meta-analysis (pooled RR, 1.39),[64,65] and the EAGLES trial found that verenicline was superior to both bupropion and nicotine patch.[66] Other studies suggest that varenicline and bupropion each have success rates of ~15-25%.[67-69] 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[70,71]
  - Aimed at treating the 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 (i.e., the transdermal patch) used in combination with a quick release product (gum, lozenge, inhaler) for acute nicotine cravings
  - No evidence of increased cardiovascular events with use after myocardial infarction
- Bupropion[72-74]
  - Effects take at least 5-7 days to manifest, thus set a quit date at least 1 week from starting therapy
  - Theoretically beneficial in patients with co-morbid depression or schizophrenia, but can make bipolar disease (mania) worse
  - Increased risk of seizure; avoid or use with extreme caution in patients at increased risk of seizure
  - Not found to be effective when studied in patients discharged after myocardial infarction[75]
- Varenicline[76]
  - Perhaps marginally superior to bupropion; no data exist comparing varenicline with long- and short-acting nicotine replacement therapy
  - Neuropsychiatric side effects initially led to a black box warning; however, no significant risk is seen in meta-analysis including subjects with mental illness,[64,65] or in the EAGLES trial, in which approximately half of the enrollees had stable chronic psychiatric disorders. The FDA subsequently withdrew this warning.[66]

— Based on current data, varenicline is likely safe in the post-myocardial infarction setting, but caution is still advised in patients at highest risk with active cardiovascular disease[77]

Figure 4: Abstinence rates at one year for medications used in smoking cessation[78]



*Placebo = counseling only; NRT = nicotine replacement therapy; Patch = nicotine patch

Alternative therapy for smoking cessation

Not enough solid data exist on which to base recommendations about the efficacy of acupuncture, hypnosis, or any other alternative therapy for smoking cessation.[79] The use of e-cigarettes has grown rapidly despite many unanswered questions about their overall safety and theoretical potential for harm reduction relative to tobacco cigarettes or efficacy in smoking cessation. A review of 4 clinical trials, 4 longitudinal studies, and 1 cross-sectional study examining the use of e-cigarettes as aids to smoking cessation concluded that e-cigarettes are not associated with successful quitting in population-based samples of smokers.[80] The authors note many limitations of current data, however, and call for larger and more rigorous studies to strengthen the evidence base.

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 any one mode of therapy.

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, quality of life, lung function, and exercise performance, and can reduce the frequency of exacerbations.[81] Bronchodilators help reduce hyperinflation, thereby increasing inspiratory capacity, relieving dyspnea, and decreasing the work of breathing, even with minimal improvement in spirometry findings.

The three classes of bronchodilators in common use are ß-agonists, antimuscarinics (also called anticholinergics), and methylxanthines, and they are used individually or in combination. The mechanisms of action of the three 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.[8] The most important effect of anticholinergic medications in patients with COPD appears to be blockade of acetylcholine's effect on muscarinic receptors, resulting in smooth muscle relaxation.[8] Methylxanthines block adenosine receptors, but may also act as nonselective phosphodiesterase inhibitors, with both actions resulting in a range of non-bronchodilator effects, the significance of which have been disputed.[8]

Both ß-agonists and anticholinergics are available as short- and long-acting agents. Combining bronchodilators of different classes (e.g., ß-agonists and anticholinergics) may be more effective than increasing the dose of a single agent.[8]

While these drugs are a mainstay of symptom control, most large long-term randomized controlled trials have failed to demonstrate a beneficial effect of bronchodilators in slowing the rate of decline in lung function in COPD.[82] A post-hoc analysis of the TORCH (Towards a Revolution in COPD Health) trial, however, did show a significant slowing of the rate of decline in lung function with the long-acting ß-agonist salmeterol compared to placebo.[83]

Short-acting inhaled bronchodilators

Short-acting bronchodilators include the ß-agonists albuterol (ProAir HFA, Proventil HFA, Ventolin, others) and levalbuterol (Xopenex, Xopenex HFA), and the anticholinergic ipratropium (Atrovent HFA, generic). They are used intermittently to relieve worsening of symptoms such as dyspnea. The use of a short-acting bronchodilator before an exercise session may reduce dynamic hyperinflation and improve exercise capacity.

Comparative effectiveness

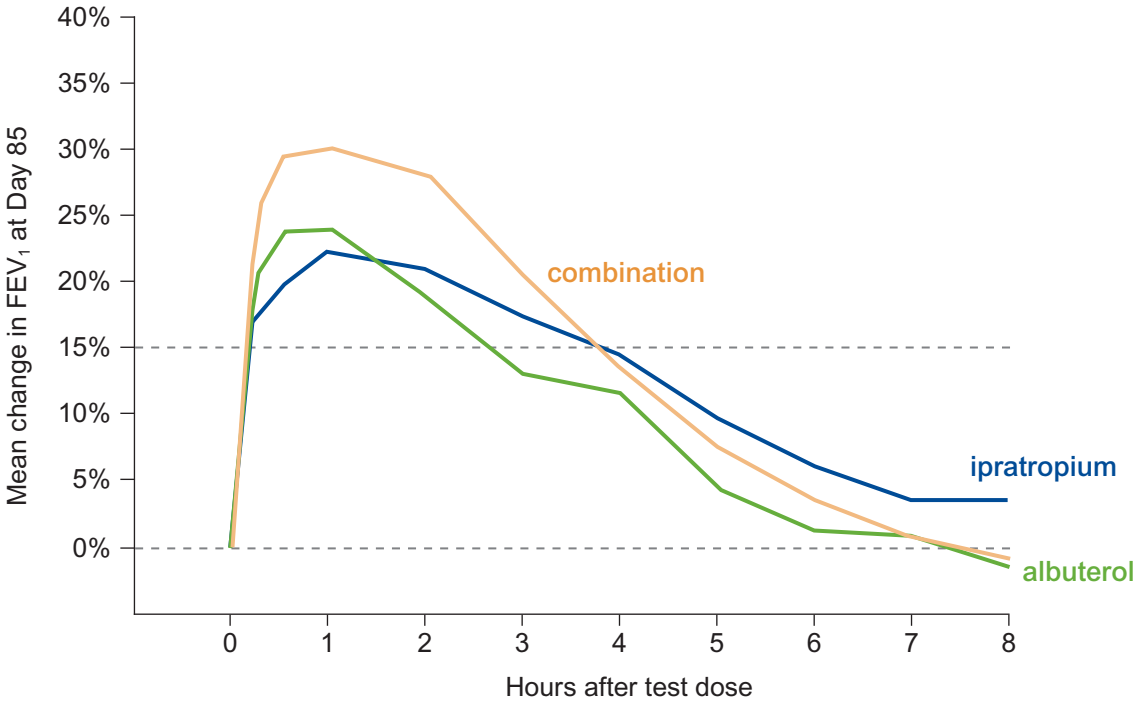
Most studies suggest that short-acting ß-agonists have equal efficacy to short-acting anticholinergics in COPD.[84] The choice between these agents depends on individual response and adverse effects.[85]

Combination therapy

If an appropriate dose of a single agent does not adequately control symptoms, consider a trial of an agent from the alternative class, or a combination of a ß-agonist with an anticholinergic.[85] 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 (Figure 5).[86]

Figure 5: Percent changes in mean FEV_1 at day 85 of COMBIVENT trial[86]



Long-acting inhaled bronchodilators

Regular treatment with long-acting bronchodilators may be more effective than intermittent or as-needed treatment with short-acting bronchodilators, and the more convenient once or twice-daily dosing may improve therapy adherence.[8,57] Long-acting inhaled bronchodilators for COPD include ß-agonists salmeterol (Serevent Diskus), formoterol (Foradil Aerolizer, Perforomist), arformoterol (Brovana), indacaterol (Arcapta), olodaterol (Striverdi) and the anticholinergics tiotropium (Spiriva), aclidinium (Tudorza) and umeclidinium (Incruse). These agents can be used to control symptoms and improve exercise capacity in patients who remain symptomatic despite treatment with short-acting medications.[85,57] A short-acting agent should be continued on an as-needed basis after initiation of a long-acting agent.[85] Long-acting ß-agonists (LABAs) and anticholinergics [or muscarinic antagonists (LAMAs)] reduce the frequency of exacerbations compared to placebo or short-acting bronchodilators.

Three large long-term studies of COPD (TORCH, POET-COPD, and UPLIFT) have significantly added to our understanding of the role of long-acting anticholinergics and ß-agonist bronchodilators in COPD. UPLIFT examined the role of tiotropium; POET-COPD compared the efficacy of salmeterol to tiotropium; and TORCH studied salmeterol and fluticasone (Flovent Diskus, Flovent HFA), alone and in combination.

UPLIFT

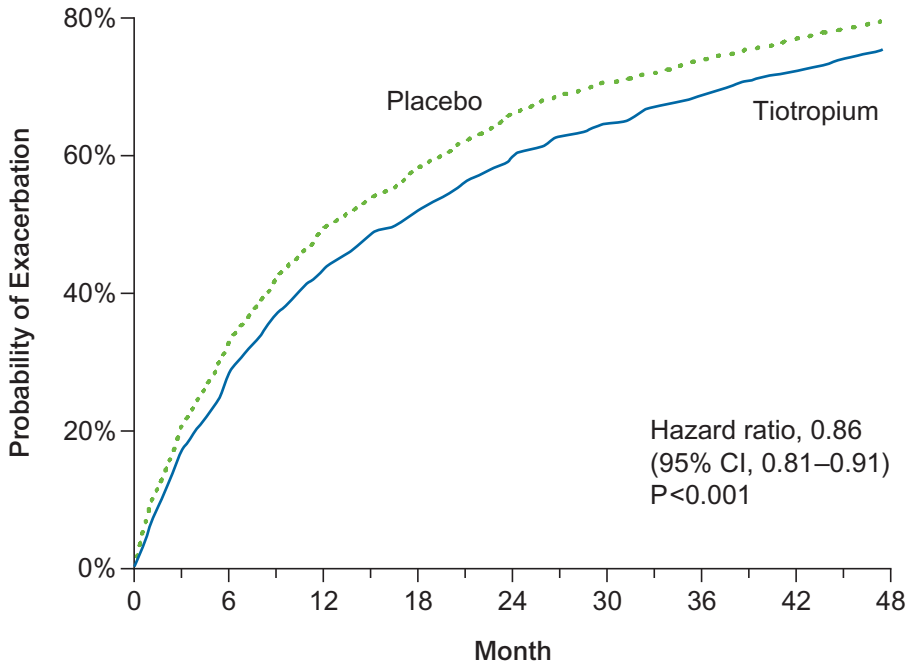
The UPLIFT study (Understanding Potential Long-term Impacts on Function with Tiotropium) enrolled nearly 6000 COPD patients over age 40. Participants were permitted to use other respiratory medications

except inhaled anticholinergic drugs and were randomly assigned to receive either tiotropium (n=2,987), or placebo (n=3,006).[87]

Follow-up was 4 years and the primary endpoints were the annual rate of decline in mean FEV_1 before and after the use of a short-acting bronchodilator. Secondary endpoints included measures of FVC, exacerbations, health-related quality of life, and mortality.

While lung function (pre- and post-bronchodilator) was significantly better with tiotropium vs. 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) (Figure 6, next page). There were no significant differences between the groups in hospitalization rates.

Figure 6: Probability of COPD exacerbation[87]



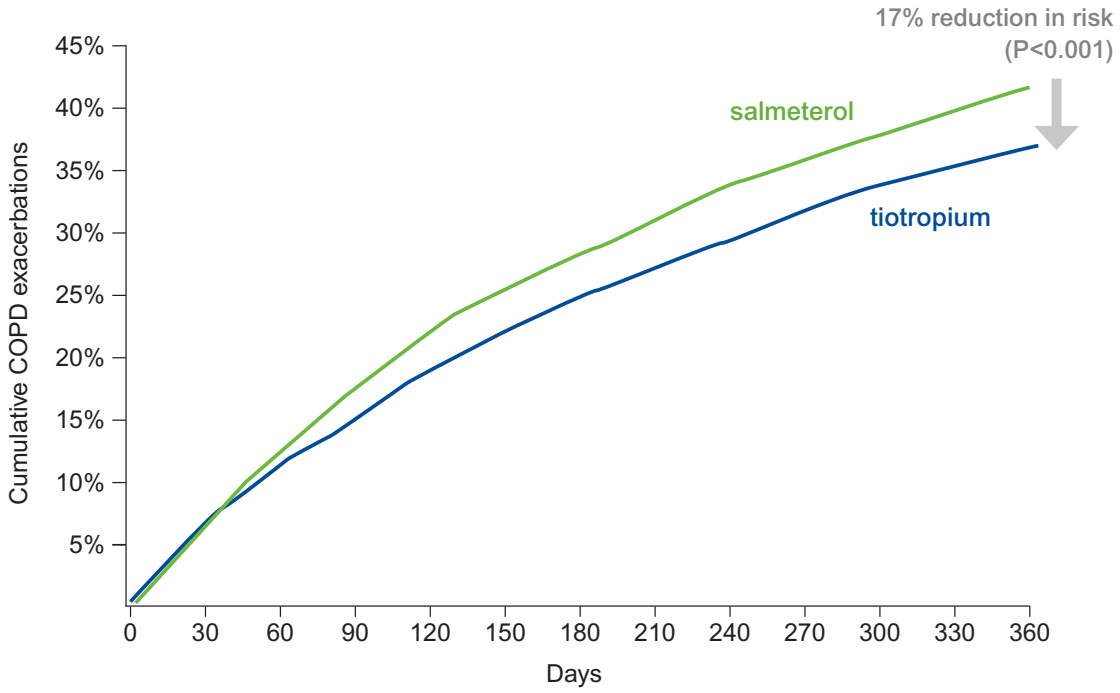
The changes in health-related quality of life on average did not meet clinical significance, nor were mortality rates statistically significantly different between the 2 groups: 14.9% in the tiotropium group and 16.5% in the placebo group (HR 0.89; 95% CI: 0.79 – 1.02).

POET-COPD

This 1-year, randomized, double-blind trial compared the effect of treatment with 18 µg of tiotropium once daily with that of 50 µg of salmeterol twice daily on the incidence of moderate or severe exacerbations in patients with moderate-to-very-severe COPD and a history of exacerbations in the preceding year.[88] 7,376 patients were randomly treated with tiotropium or salmeterol. Patients were allowed to continue their usual medications for COPD, except for anticholinergic drugs and long-acting beta agonists. The time to the first exacerbation (the primary endpoint) was increased by 42 days with tiotropium as compared with salmeterol (187 days vs. 145 days), corresponding to a 17% reduction in risk (HR 0.83;

95% CI: 0.77 – 0.90; p<0.001) (Figure 7). Tiotropium also increased the time to the first severe exacerbation (HR 0.72; 95% CI: 0.61 – 0.85; p<0.001), reduced the annual number of moderate or severe exacerbations (HR 0.64 vs. 0.72; rate ratio 0.89; 95% CI: 0.83 – 0.96; p=0.002), and reduced the annual number of severe exacerbations (0.09 vs. 0.13; rate ratio 0.73; 95% CI: 0.66 – 0.82; p<0.001). Overall, the incidence of serious adverse events and of adverse events leading to the discontinuation of treatment was similar in the two study groups. These results suggest that, in patients with moderate-to-very-severe COPD, tiotropium is more effective than salmeterol in preventing exacerbations. Treatment effect was independent of inhaled corticosteroid use, and exacerbation frequency was low in both groups.

Figure 7: Probability of a first exacerbation (POET-COPD)[88]



TORCH

The TORCH study examined the effect of salmeterol/fluticasone propionate combination therapy and its individual components on the survival of COPD patients.[89] TORCH enrolled 6,112 patients with moderate-to-severe COPD and randomly assigned them to treatment with:

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

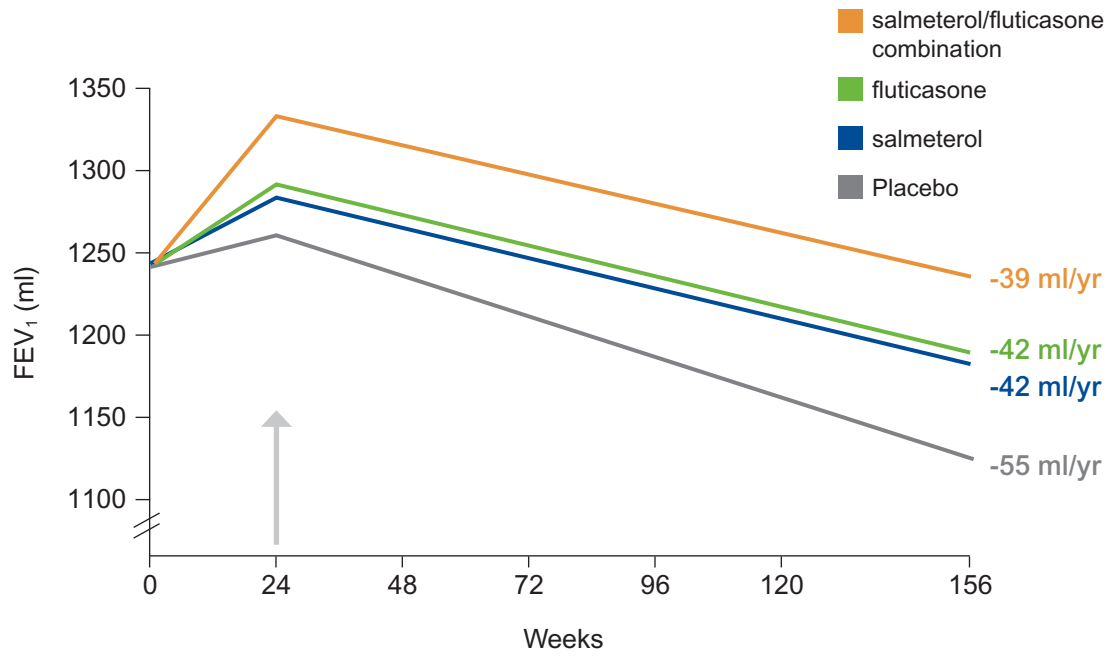
Trial duration was 3 years and the primary endpoint was all-cause mortality. Secondary endpoints were rate of exacerbations and health-related quality of life.[89] Table 4 summarizes results comparing the LABA salmeterol with placebo (additional results are discussed later in this guide).

Table 4: TORCH results, salmeterol vs. placebo[89]

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

A post-hoc analysis of the TORCH study found that the adjusted rate of decline in FEV_1 was 55 mL/year for placebo and 42 mL/year for salmeterol (difference = 13 mL/year; 95% CI: 5 – 22; p=0.003) (Figure 8). This was the first time that a pharmacologic therapy was shown to slow the decline of lung function in patients with COPD, although this finding has not been consistently demonstrated and its clinical importance is unclear.[83]

Figure 8: TORCH – rate of decline of FEV_1 [89]



Choice of initial bronchodilator

A Cochrane review of seven studies found that tiotropium was more effective than LABAs in preventing exacerbations, but this was complicated by a high degree of heterogeneity and differences among the LABA types (studies included salmeterol, indacaterol, and formoterol).[90] The INVIGORATE trial of 3,444 patients randomized to the newer LABA indacaterol vs. tiotropium, had similar findings for a reduction in exacerbations, though the number of events overall was small.[91] Few studies have compared specific therapies, and most guidelines have concluded that there is insufficient evidence to recommend a specific

long-acting bronchodilator.[92,93] Specific exceptions may be made for individual patients; for example, patients with the COPD asthma overlap syndrome (ACOS) should likely not receive LABA monotherapy.

Combination therapy: LABA + LAMA vs. either alone

A Cochrane review in 2015, including 10 studies with 10,894 patients found that on average, tiotropium (Spiriva) in combination with a LABA (including olodaterol, indacaterol, formoterol, and salmeterol) resulted in a modest improvement lung function and quality of life as measured by the St. George's Respiratory Questionnaire (SGRQ) compared to either medication alone.[90] There was also a reduction in exacerbations with tiotropium added to a LABA, but not vice versa, and insufficient evidence to determine risks and benefits of the different LABAs.[90] The FLIGHT1 and FLIGHT2 studies[94] evaluated a LABA/LAMA (indacaterol / glycopyrrolate; Utibron Neohaler) and its monocomponents in 2,038 patients. Combination therapy led to improvement in FEV_1, SGRQ, and reduction in rescue medication use. Additional combination therapies are approved in the US, including the LABA vilanterol combined with the LAMA umeclidinium (Anoro Ellipta), the LAMA glycopyrrolate and LABA formoterol (Bevespi Aerosphere), and the anticholinergic tiotropium with the LABA olodaterol (Stiolto Respimat). These preparations do not yet have a safety track record adequate to warrant a recommendation for their use in place of existing products.

Based on these and other data, a number of guidelines advocate combined bronchodilator therapy for patients who do not respond well to initial monotherapy with an anticholinergic or ß-agonist.[8]

Safety

In November 2005, the FDA issued an alert that LABAs have been associated with an increased risk of severe asthma exacerbations and asthma-related death.[95] LABAs now carry a black box warning that they may increase the risk of asthma-related death, and that they should be used to treat asthma only if symptoms are not controlled on low-to-medium dose inhaled corticosteroids, or if disease severity warrants initial treatment with two maintenance drugs. The TORCH study, however, did not find an increased risk of mortality with salmeterol, alone or in combination with fluticasone, compared to placebo in patients with COPD.[89]

A 2008 meta-analysis examined the effect of inhaled anticholinergics (ipratropium or tiotropium) on adverse cardiovascular (CV) outcomes in patients with COPD.[96,97] The study included randomized controlled trials of any inhaled anticholinergic for COPD that had data for ≥30 days of treatment and reported on CV events. The analysis included 17 trials (12 tiotropium; 5 ipratropium) enrolling 13,645 patients. Inhaled anticholinergics were associated with a significantly increased relative risk of cardiovascular death (up by 92%), MI (up by 52%), and a composite of these that also included stroke (up by 60%) in patients with COPD. There was also a 29% relative increase [0.5% absolute difference] in all-cause mortality (p=0.05).

These results should be interpreted cautiously, however, because the meta-analysis did not include data from either the UPLIFT study, which showed no increase in all-cause mortality with tiotropium compared to placebo (actually a trend towards lower rate of cardiovascular adverse events or mortality), or the POET-COPD study, which showed no increase in CV risk of tiotropium compared with salmeterol. Any risk associated with these agents should be balanced against their potential benefits (symptom improvement, increased exercise capacity, reduction in the frequency of exacerbations, and fewer hospitalizations because of exacerbations).

Summary of efficacy of inhaled bronchodilators in COPD

Table 5: Inhaled bronchodilators in COPD

Outcomes	Short-acting β-agonist	Long-acting β-agonist	Short-acting anticholinergic	Long-acting anticholinergic
FEV_1 improvement	Y	Y	Y	Y
Symptom relief	Y	Y	Y	Y
Reduce exacerbations	N	Y	Y	Y
Improve exercise tolerance	Y	Y	Y	Y
Slow progression of disease	N	N	N	N
Reduce mortality	N	N	N	N

Y = Yes; N = No, or evidence lacking/inconclusive

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 long-acting anticholinergics (tiotropium) versus beta-agonists, though there is substantial heterogeneity in the findings of individual studies. These medications have not been conclusively shown to slow the progression of disease or reduce mortality.

Inhaled corticosteroids

Inflammation in COPD appears to be more resistant to corticosteroids than in asthma. As a result, inhaled corticosteroids (ICS) should not be routinely used as a first-line medication in most patients with COPD.[98]

Rate of decline in lung function

It is unclear whether ICS can slow the rate of lung function decline in COPD. Meta-analyses have produced conflicting results, with one study finding no significant benefit, and another finding that ICS did slow the rate of decline (by 7.7 mL/year; 95% CI: 1.3 – 14.2; p=0.02).[99,100] A 2012 Cochrane review found that although ICS resulted in a small improvement in lung function initially, long-term use (>6 months) did not slow the rate of decline in lung function.[101] A post-hoc analysis of the 3-year TORCH study, however, found that the adjusted rate of decline in FEV_1 was 55 mL/year for placebo and 42 mL/year for fluticasone (difference = 13 mL/year; 95% CI: 5 – 22; p=0.003).[83] Similar small differences were also seen in the SUMMIT trial (difference = 8 mL/year; 95% CI: 1-14).[102]

Impact on exacerbations

Despite the unclear impact on lung function, several trials have demonstrated that ICS therapy (alone or in combination with a LABA) reduces the frequency of COPD exacerbations in patients with an FEV_1

<50% predicted. A 2007 Cochrane review found that ICS therapy reduces the rate of exacerbations and the rate of decline in quality of life.[103] The TORCH study showed that the combination of salmeterol and fluticasone significantly reduced the annual rate of exacerbations from 1.13 to 0.85 (p<0.001).[89]

Mortality

Studies of the impact of ICS on mortality for patients with stable COPD have yielded conflicting results. A 2005 meta-analysis of 7 placebo-controlled trials found that ICS reduced mortality in COPD (HR 0.73; 95% CI: 0.55 – 0.96).[104] The TORCH study in 2007, however, did not demonstrate a reduction in mortality with ICS compared to placebo.[89] A 2008 meta-analysis of 11 trials (14,426 participants) comparing ICS therapy for ≥6 months with non-steroid inhaled therapy in patients with COPD found no difference in 1-year all-cause mortality (RR treatment to control 0.86; 95% CI: 0.68 – 1.09; p=0.20).[105] The lack of survival benefit in this study is consistent with a previous meta-analysis.[106] Similarly, a 2012 Cochrane review including 9 trials found that long-term use of ICS (>6 months) did not reduce mortality rates (OR 0.98; 95% CI: 0.83 – 1.16).[101]

Adverse effects

The TORCH study found a significantly increased incidence of pneumonia with fluticasone compared to placebo (18.3% vs.12.3%; p<0.001).[89] A 2008 meta-analysis found that ICS therapy was associated with a significantly higher incidence of pneumonia (RR for treatment compared to control group, 1.34; 95% CI: 1.03 – 1.75; p=0.03).[105] Similarly, a 2009 meta-analysis found that ICS use significantly increased the risk of pneumonia compared to treatment without ICS (RR 1.60; 95% CI: 1.33 – 1.92; p<0.001), but did not significantly increase the risk of pneumonia-related mortality or overall mortality.[107]

A 2012 Cochrane review also found an increase in pneumonia, and reported an increased risk of local effects such as oropharyngeal candidiasis.[101] Systemic effects of prolonged use were less clear, with several studies showing no change in fracture rate or bone mineral density, but one study showing a reduction in bone mineral density. Overall, the longer term systemic effects (>3 years) of ICS are not clearly defined.[101]

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.

Inadequate inhaler technique is common.[108] It has been found to occur in about 70% of patients, resulting in inadequate delivery of medication.[109] 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.[57] Devices such as the Turbuhaler and Accuhaler require a level of inspiratory capacity that may be unachievable in severe COPD.

Many patients benefit from using a metered dose inhaler (MDI) with a spacer, especially if severe disease is present. Drug delivery with a nebulizer is more expensive and no more effective than an MDI with a spacer. Patients unable to use an MDI, however, may need to use a nebulizer.

Counseling the patient using the package insert, as well as physically demonstrating the device, can significantly improve inhaler technique.[110] 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.[109] In addition, review inhaler use at the time of any exacerbation.

A description of inhaler devices with practical instructions on their use is provided in Appendix 2. 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 one delivery mode is more effective than another.[111-114]

COPD pharmacologic management and mortality

Death related to cardiovascular disease is the most common cause of mortality in patients with symptomatic moderate COPD (i.e., COPD GOLD group B), but no current pharmacologic treatments for COPD significantly decrease all-cause mortality.[115]

The Study to Understand Mortality and MorbidiTy (SUMMIT) trial was a double-blind placebo-controlled randomized trial looking at the effect of once-daily treatment with the inhaled corticosteroid fluticasone furoate (100 µg), the long-acting ß$_2$ agonist vilanterol (25 µg), or a combination of fluticasone furoate plus vilanterol on mortality in 16,485 patients with symptomatic moderate COPD and high cardiovascular risk.[102] The primary outcome measure was all-cause mortality.

The probability of death from any cause did not differ between treatment groups. Compared with placebo, all-cause mortality was unaffected by combination therapy (HR 0.88 [95% CI 0.74–1.04]; 12% relative reduction; p=0.137) or the components (fluticasone furoate, HR 0.91 [0.77–1.08], p=0.284; vilanterol, 0.96 [0.81–1.14], p=0.655). Compared with placebo, treatment with fluticasone furoate, vilanterol, or the combination also did not affect a secondary composite cardiovascular endpoint (cardiovascular death, myocardial infarction, unstable angina, stroke, and transient ischemic attack).

These results support the existing GOLD recommendations that long-acting bronchodilators (long-acting ß$_2$ agonist or long-acting muscarinic antagonists) remain the first choice of treatment for patients with symptomatic moderate COPD.[116]

Combined inhaled bronchodilator/ICS therapy

LABA + ICS vs. placebo

Results from the TORCH study for LABA + ICS combination therapy compared to placebo are shown in Table 6.[89]

Table 6: TORCH results: Combination therapy vs. placebo [89]

Outcomes	Effect Sizes
Mortality rate	12.6% vs. 15.2% for placebo (HR 0.82; 95% CI: 0.681 – 1.002; p=0.052)
Health-related quality of life score (negative is better)	-3.1; (p<0.001)
Annual rate of moderate or severe exacerbations	0.85 vs. 1.13 for placebo (HR 0.75; 95% CI: 0.69 –0.81; p<0.001)
FEV_1 (post bronchodilator)	+92 mL; (p<0.001)
Pneumonia rate	19.6% vs. 12.3% for placebo; (p<0.001)

A post-hoc analysis of the TORCH study found that the adjusted rate of decline in FEV_1 was 55 mL/year for placebo and 39 mL/year for salmeterol plus fluticasone (difference = 16 mL per year; 95% CI: 7 – 25; p<0.001).[83] Recently, the Salford Lung Study completed a trial of ICS/LABA (fluticasone/vilanterol) compared with usual care in 2799 patients.[117] This study included a broader range of patients: age >40, diagnosis of COPD with one or more exacerbations in the prior 3 years, and on maintenance therapy, and did not exclude subjects coexisting cardiac disease (26%) or asthma (22%). A pre-defined subset of subjects with one or more exacerbations in the past year (2269; 90% with a CAT ≥10) supported the primary outcome of reduced exacerbations (8.4% reduction, 95% CI: 1.1 – 15.2; p=0.02).

A Cochrane review compared the efficacy of combined LABA and ICS against placebo in COPD.[118] Fluticasone/salmeterol and budesonide/formoterol both reduced the rate of exacerbations compared with placebo. Pooled analysis of both combination therapies found a 26% reduction in the frequency of exacerbations compared with placebo (RR 0.74; 95% CI: 0.7 – 0.8). Treatment with combination therapy would lead to a reduction of one exacerbation every 2-4 years. There was an overall reduction in mortality, with a number needed to treat of 42 for 3 years to prevent 1 death, however this finding resulted predominantly from data from the TORCH trial involving fluticasone/salmeterol, and further studies on budesonide/formoterol are needed. There was an increase in the risk of pneumonia with combination therapy, with a number needed to harm of 17 over 3 years for 1 additional case of pneumonia.

LABA + ICS vs. ICS alone

The TORCH study found that mortality with LABA/ICS (salmeterol/ fluticasone) combination therapy was significantly reduced compared to fluticasone alone (HR 0.77; 95% CI: 0.64 – 0.93; p=0.007). The annual rate of moderate or severe exacerbations, post-bronchodilator FEV_1, and health-related quality of life were all significantly improved with combination therapy compared to fluticasone alone. There was no significant difference in the probability of fractures between the groups.[89]

A Cochrane review compared the efficacy of combined ICS and LABA with ICS alone in the treatment of COPD.[119] Combination therapy reduced exacerbations by 13% compared to ICS monotherapy (RR 0.87; 95% CI: 0.80 – 0.94; p=0.0008). There was a 22% reduction in mortality with combined treatment (OR 0.78; 95% CI: 0.64 – 0.94), primarily based on the results of TORCH. Quality of life, lung function improvement, and withdrawals due to lack of efficacy also favored combination treatment. Adverse event profiles were similar between the two groups, but the review pointed out that ICS have been associated with an increased risk of pneumonia.

LABA + ICS vs. LABA alone

The TORCH study found that mortality with LABA/ICS (salmeterol/ fluticasone) combination therapy was not significantly reduced compared to salmeterol alone (HR 0.93; 95% CI: 0.77 – 1.13; p=0.48). However, the annual rate of moderate or severe exacerbations, post- bronchodilator FEV_1, and quality of life were significantly improved with combination therapy compared to salmeterol alone. There was no significant difference in the probability of fractures between the groups.[89]

A Cochrane review compared the efficacy in COPD of combined ICS and LABA compared to LABA alone.[120] Combination therapy reduced exacerbation rates by 24% compared to LABA alone (OR 0.82; 95% CI: 0.71– 0.95), but the finding was rated as lower quality evidence due to heterogeneity and risk of bias from withdrawal rates. There was no significant difference in mortality between combination therapy and LABA monotherapy. Pneumonia occurred more frequently with combination therapy than with LABA alone (OR 1.59; 95% CI: 1.35 – 1.86). There was no significant difference in hospitalization. Combination therapy was more effective than LABA in improving quality of life, and pre-dose and post-dose FEV_1.

There has been increasing interest in the use of biomarkers to predict patients who respond to corticosteroids, most notably eosinophil counts. In a post-hoc analysis of two LABA vs. LABA/ICS (vilanterol and fluticasone) studies totaling 3177 patients, with FEV_1 <70% predicted and at least one exacerbation over the past year, patients with higher blood eosinophil counts were more likely to have exacerbations and benefit from ICS.[121] In patients with eosinophil counts of ≥2% there was a 29% reduction (0.91 from 1.28), but in those with counts <2%, the reduction was 10% (0.79 vs. 0.89; p=0.28). The pattern of greater reduction in exacerbations from ICS was also seen in another post-hoc analysis of a different ICS/LABA study.[122]

LABA + ICS vs. LAMA

The INSPIRE (Investigating New Standards for Prophylaxis in Reducing Exacerbations) study compared the efficacy of the tiotropium with salmeterol/fluticasone combination therapy in preventing exacerbations and related outcomes in severe and very severe COPD.[123] The 2-year study enrolled 1,323 patients and randomly assigned them to treatment with tiotropium 18 mcg once daily, or salmeterol/ fluticasone propionate 50/500 mcg twice daily.

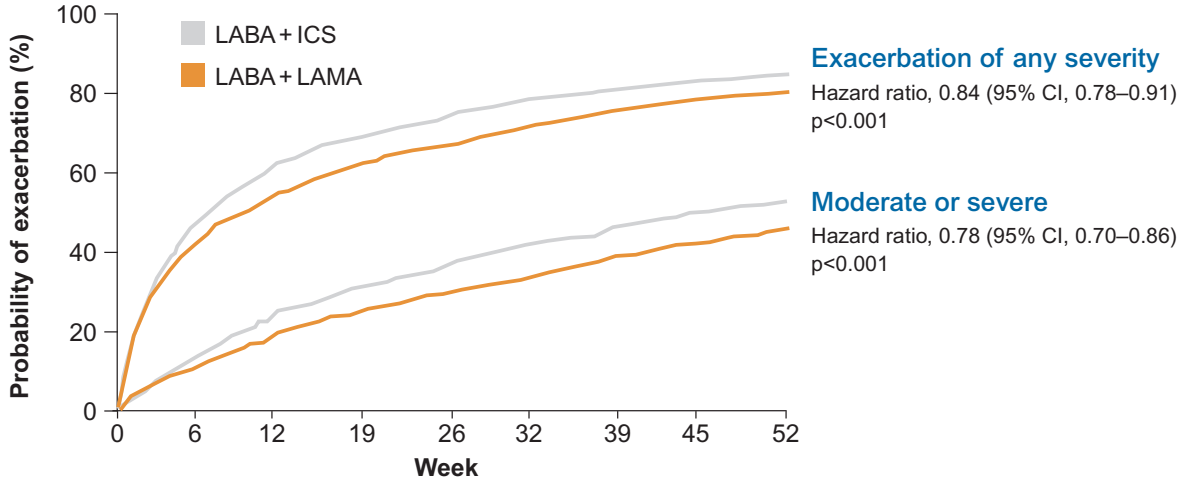
The main outcome measure was exacerbation rate. Other outcomes included health, as measured by the SGRQ, mortality, adverse events, and study withdrawal. The annual exacerbation rate was not significantly different between the 2 groups (1.28 in the salmeterol/fluticasone propionate group and 1.32 in the tiotropium group; RR 0.967; 95% CI: 0.84 – 1.12; p=0.656). The SGRQ total score was lower at 2 years on salmeterol/fluticasone propionate versus tiotropium, but the difference (2.1 units; 95% CI: 0.1 – 4.0; p=0.038), while statistically significant, is of questionable clinical importance. Mortality was significantly lower in the salmeterol/fluticasone propionate group (3% of patients in this group died compared with 6% in the tiotropium group, p=0.032). There was a 29% greater chance of withdrawing from the study with tiotropium than with salmeterol/fluticasone (p=0.005). More pneumonias were reported in the salmeterol/fluticasone propionate group relative to tiotropium (p=0.008).

LABA + ICS vs. LABA + LAMA

The FLAME trial was a double-blind non-inferiority trial that randomized 3,362 COPD patients with at least GOLD Grade 2 obstruction (FEV_1 <60% predicted), mMRC ≥2, and at least one exacerbation in the past year (corresponding to 75% GOLD D and 25% GOLD B) for 52-weeks to either LABA indacaterol

with the LAMA glycopyrronium or the LABA salmeterol with fluticasone.[124] The primary outcome was all COPD exacerbations. The LABA/LAMA combination resulted in a 11% decrease (3.59 vs. 4.03, rate ratio 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 (0.98 vs. 1.19, rate ratio 0.83; 95% CI: 0.75 – 0.91). Differences in lung function and quality of life measures also favored LABA/LAMA. Issues with this study include dosing (US-approved dosing does not match what was used in this study).

Figure 9: Probability of exacerbation[124]



Triple therapy

TRINITY was a randomized, double-blind controlled trial comparing fixed triple therapy (LAMA [glycopyrronium bromide]/LABA [formoterol fumarate, FF]/ICS [extrafine beclomethasone dipropionate, BDP]) with the LAMA tiotropium alone, and BDP/FF plus tiotropium (open triple therapy).[125] Most of the patients in the trial had were selected for higher risk of exacerbations under prior GOLD criteria, with a history of exacerbations and severe COPD by spirometric criteria (FEV_1 <50%). The primary outcome measure was moderate to severe COPD exacerbation rate after 52 weeks of treatment.

Moderate-to-severe exacerbation rates were 0.46 (95% CI 0.41–0.51) for fixed triple, 0.57 (0.52–0.63) for tiotropium, and 0.45 (0.39–0.52) for open triple; fixed triple was superior to tiotropium (rate ratio 0.80 [95% CI 0.69–0.92]; p=0.0025). Thus, compared with tiotropium, fixed triple therapy showed a 20% reduction in the rate of moderate-to-severe COPD exacerbations together with an improvement in lung function, and was non-inferior to open triple therapy. Adverse event rates were comparable across study arms: 594 (55%) patients with fixed triple, 622 (58%) with tiotropium, and 309 (58%) with open triple.

TRINITY demonstrates that triple therapy can be effective in patients in reducing exacerbations in those with severe spirometric COPD (FEV1 <50%) and a history of exacerbations. However, It should be noted that only about 20% of the patients examined had had at least two exacerbations or more than one hospitalization (GOLD D).[126]

TRILOGY was a randomized, multicenter study of 1,368 subjects with severe COPD (FEV_1 <50% predicted), at least 1 COPD exacerbation requiring any of systemic steroids, antibiotics, or hospitalization in the last year, and a CAT (COPD assessment test) ≥10.[127] Patients were started with a run-in period of

ICS-LABA (beclomethasone and formoterol) for two weeks, and then randomized to either continue this therapy or step up to triple therapy, including glycopyrronium. There were three co-primary endpoints: pre-dose FEV1, post-dose $FEV_{1,}$ and dyspnea index, all measured at 26 weeks. Secondary outcomes included COPD exacerbations at 52 weeks.

There were statistically significant differences favoring triple therapy in all co-primary endpoints, though dyspnea was not different at 6 months. In addition, there was a decrease in moderate-to-severe exacerbations (35% to 31%, adjusted annual rate 0.53 vs 0.41). A Cochrane review included six studies with 1902 participants and found a reduction in hospital admissions (OR 0.61; 95% CI: 0.40 – 0.92) for ICS/LABA + tiotropium versus tiotropium alone, but was unable to evaluate the additional benefit of adding tiotropium to LABA/ICS.[128] These studies help support the recommendations for triple therapy in the most severe GOLD categories.

However, some data suggest that it may be safe to withdraw inhaled corticosteroids from a triple-therapy regimen. In the WISDOM (Withdrawal of Inhaled Steroids during Optimized Bronchodilator Management) trial, 2,845 patients with severe COPD (GOLD Grade 3-4, FEV_1 <50% predicted) and at least one exacerbation in the prior year 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.[129] The time to first moderate or severe COPD exacerbation met prespecified noninferiority criteria (hazard ratio, 1.06, CI 0.94 to 1.19), with no changes in dyspnea. There was, however, a slight decrease in lung function (FEV_1 43mL at week 52) with ICS withdrawal, and minor changes in health status as measured by the SGRQ.[129]

Recommendations for therapy with inhaled steroids

The 2017 GOLD guidelines recommend adding inhaled steroids to other regimens for patients with frequent exacerbations (Groups C or D).[8] ICS should not be given as monotherapy. ICS may also be considered in patients who do not have frequent exacerbations, but remain symptomatic despite optimal bronchodilator therapy, or who appear to have an asthmatic component to their disease.

Advise patients to rinse their mouth and throat with water after each use of an ICS to minimize oral thrush, hoarse voice, and systemic absorption.

Table 7: Summary of ICS efficacy in COPD

Outcomes	ICS
FEV_1 improvement	Y
Symptom relief	Y
Reduce exacerbations	Y
Improve exercise tolerance	N
Slow progression of disease	N
Reduce mortality	N

Y=Yes, N=No, or evidence lacking/inconclusive

BOTTOM LINE: Based on TORCH and other studies, inhaled corticosteroids should not be used as monotherapy. In patients on long acting bronchodilator(s), adding inhaled corticosteroids may improve symptoms and reduce the frequency of exacerbations in severe disease. ICS improve lung function in the short term. Consider use of ICS in severe disease with frequent

exacerbations, or in patients who remain symptomatic despite optimal bronchodilator therapy. ICS can increase the risk of pneumonia but not mortality. Triple therapy (i.e., LABA/LAMA/ICS) may be effective in patients defined as GOLD severity D.

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. Phosphodiesterases are a large family of enzymes involved in the regulation of numerous physiological processes, with 11 isoenzymes identified to date.[130] Inhibitors of the PDE_4 isoenzyme have anti-inflammatory and bronchodilatory properties in the lungs.[131] Two PDE_4 inhibitors have been extensively studied: cilomilast and roflumilast (Daliresp). Roflumilast is approved in the US for the indication of reducing COPD exacerbations. The original submission of cilomilast to the FDA in 2002 was not approved and further long-term studies were requested.[132]

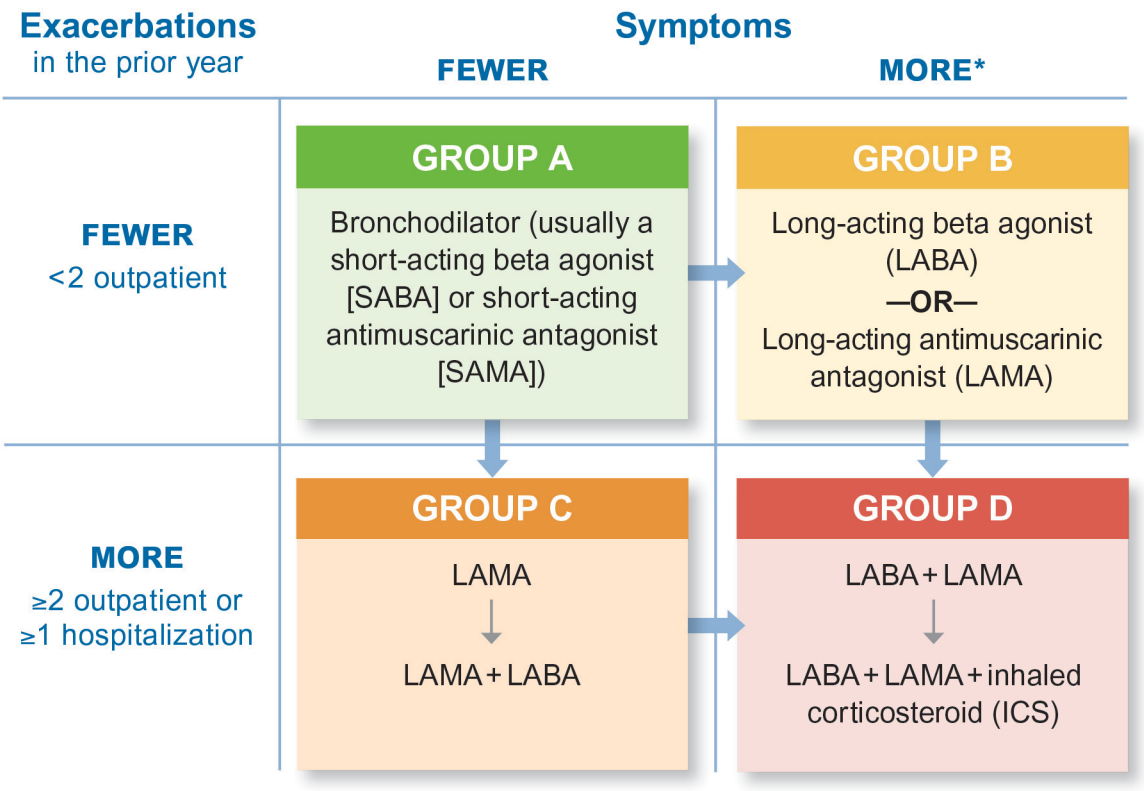
Numerous studies of both cilomilast and roflumilast have been conducted. A 2013 Cochrane Review identified 29 published and unpublished placebo-controlled trials on cilomilast and roflumilast that included 19,111 COPD patients with a wide range of disease severities.[133] The meta-analyses show mixed results for benefit and harm outcomes: both cilomilast and roflumilast reduced the risk for exacerbations (overall OR 0.77; 95% CI: 0.71 – 0.83) and led to improvements of lung function of unclear clinical relevance compared to placebo, and symptoms, health-related quality of life and exercise capacity were either minimally improved or unaffected.

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 baseline ICS-LABA; background tiotropium was allowed.[134] 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, PDE4 inhibitors are generally recommended as an adjunct to other treatment.

BOTTOM LINE: PDE_4 inhibitors should be reserved for patients with an FEV_1 <50%, symptoms of chronic bronchitis, and frequent exacerbations despite the use of long-acting bronchodilators, who also are not underweight and have no GI contraindications.

Putting it all together: Pharmacological therapies at various stages of stable COPD

Table 8: Pharmacological management of COPD[8]



Optional/alternative therapy:
Group A: SABA+SAMA or LAMA or LABA
Group B: LABA+LAMA
Group C: LABA+ICS
Group D: LAMA or LABA+ICS or triple therapy+roflumilast or triple therapy+azithromycin

Other medications

Methylxanthines

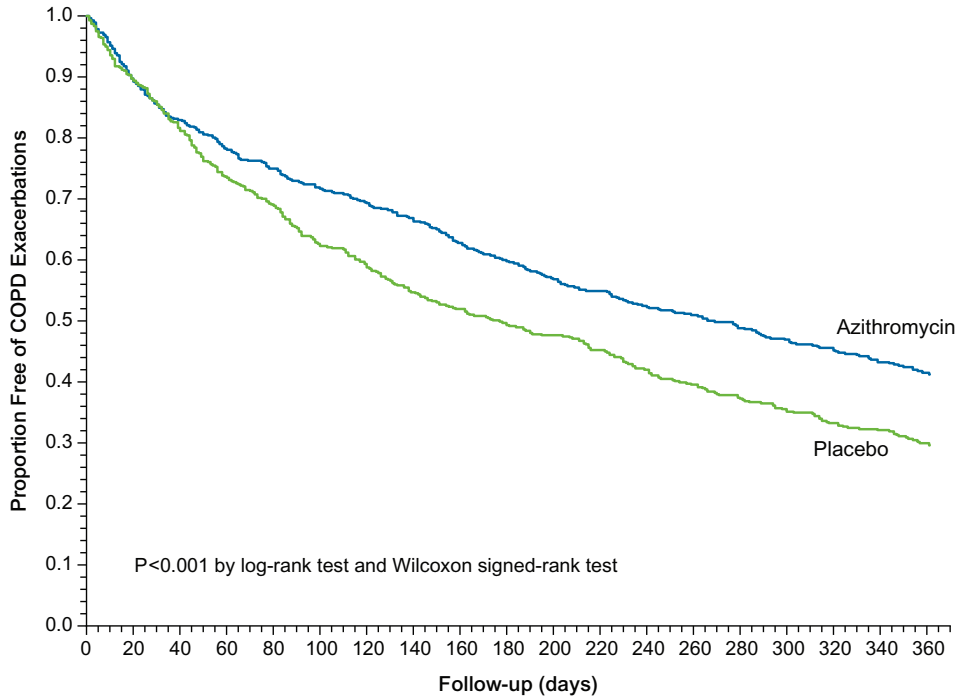
Methylxanthines may be effective for selected patients with stable disease. Theophylline (Theo-24, Elixophyllin, Uniphyl) is the most-commonly used methylxanthine in this patient population, with aminophylline used rarely. Relatively small studies have shown improvements in dyspnea, exercise capacity, respiratory mechanics, respiratory muscle strength, lung function, and exacerbations. Theophylline's mechanisms of actions are not entirely clear, and may be related to its stimulant or anti-inflammatory effects.[135,136] Theophylline may be used if a patient is unable to use inhaled therapy, or if

other bronchodilator therapy has failed to adequately control symptoms, especially at night. The drug has a narrow therapeutic index and can be difficult to manage. It requires careful titration and routine plasma monitoring if used chronically, because of the risk of serious cardiovascular and central nervous system adverse effects. Frequent dose adjustments are required in many patients, including smokers and the elderly.[137] All studies showing efficacy of theophylline in COPD were with slow-release preparations. Theophylline is not a recommended treatment for COPD exacerbations.[138] Aminophylline (generic) is a salt of theophylline; 1 mg aminophylline is equivalent to 0.8 mg theophylline.

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 3 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.[139] 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.[140] Patients treated with erythromycin had shorter duration exacerbations compared with placebo. There were no differences in FEV_1 between the antibiotic and placebo groups.[140]

Figure 10: Exacerbation-free patients on azithromycin vs. placebo[141]



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.[141] 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 10). This effect was additive to other therapies for COPD, since >80% of patients were on inhaled corticosteroids, a LABA, an anticholinergic, or a

combination of these treatments. 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.[142,143] 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.[144,145]

Oral corticosteroids

A 2009 Cochrane review concluded that no evidence supports the routine long-term use of oral steroids in patients with stable COPD. This treatment should generally be avoided because of the significant increased risk of adverse effects such as osteoporosis, hypertension, and hyperglycemia.[146,147] However, acute use of oral steroids can have a place in managing exacerbations (see page 37).

Mucolytics

A Cochrane review (28 trials, n=7,164) found that in adults with stable chronic bronchitis or COPD, regular treatment with oral mucolytics, usually n-acetylcysteine (NAC), was associated with a reduction of 0.36 exacerbations per year.[148] The most recent large study, the Chinese PANTHEON trial found that NAC 600mg twice daily reduced the risk of exacerbations (RR 0.78 after one year).[149] However, issues such as a high dropout rate, and inclusion of never smokers and subjects not 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.[150]

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.

Non-pharmacological interventions for COPD

Long-term home oxygen therapy

Long-term administration of oxygen (>15 hours per day) can reduce mortality in patients with chronic hypoxemia (PaO_2 <55 mmHg), though it may not improve survival in patients with less severe hypoxemia or in those with only nocturnal oxygen desaturation.[8,151,152] The benefits of oxygen therapy in the presence of hypoxemia outweigh the risks associated with its use (i.e., oxygen toxicity, CO_2 retention, physical hazards).[5] Patients with hypoxemic respiratory failure have a three-year survival rate of only

about 40%.[34] Long-term oxygen administration increases survival to 50% with nocturnal treatment alone, and to 60% with oxygen administration for >15 hours a day.[153]

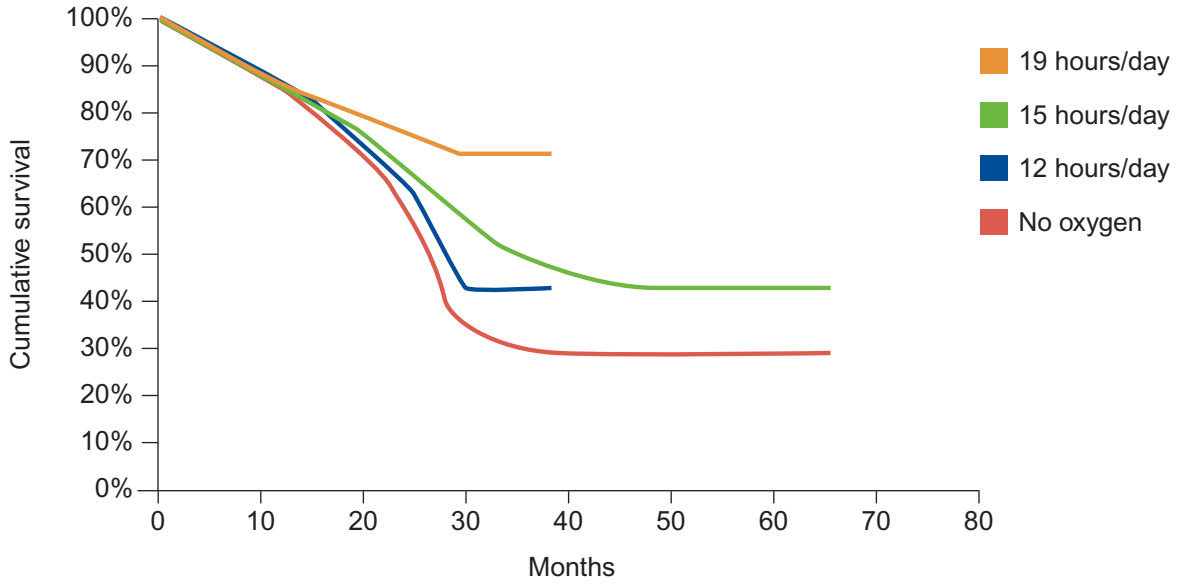
Long-term oxygen should be started in patients with stable disease on a full medical regimen, if they have:

- PaO_2 ≤55 mmHg or SaO_2 ≤88%[8,5]
- PaO_2 of 55–59 mmHg with evidence of pulmonary hypertension, *cor pulmonale*, peripheral edema, polycythemia (hematocrit >55%), or impaired mental status[85,5]
- PaO_2 ≥60 mmHg with exercise desaturation, sleep desaturation not corrected by continuous positive airway pressure (CPAP), or severe dyspnea responding to O_2[5]

The goal is to maintain SaO_2 >90% during rest, sleep, and exercise.[5] A Cochrane review found that patients with COPD can exercise longer and have less shortness of breath when using oxygen during exercise.[154]

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.[155] 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.

Figure 11: Trials of long-term oxygen therapy[153,34]



A new 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) delayed the time to readmission or death compared to patients not receiving ventilation, 4.3 months and 1.4 months, respectively.[156] Noninvasive ventilation reduced annual risk of the 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.

A 2013 Cochrane reviewed seven studies of noninvasive ventiliation with 245 participants finding no consistent or significant effects on gas exchange, exercise tolerance, quality of life, lung function, or other outcomes.[157] Two studies from 2014, not included in the Cochrane review (Kohnlein et al., and Struik et al.) included about 200 patients each and reported conflicting results.[158,159] Many trials, such as the latest Murphy, et al. article, did not assess for undiagnosed sleep apnea, which, when treated, improves survival and the risk of hospitalization.[8] The patient populations included in these trials are also specific, with about 6% of patients admitted to the hospital and requiring noninvasive ventilation. No guidelines or professional recommendations yet guide the use of home noninvasive ventilation.[8]

Immunization

A recent Cochrane review found that influenza vaccination reduces the frequency of exacerbations in COPD patients,[160] and annual vaccination against influenza is recommended.[8] Pneumococcal polysaccharide vaccination is indicated for all adults with chronic pulmonary disease (see the 2017 adult immunization schedule at cdc.gov/vaccines/schedules/hcp/adult.html). Vaccination against pneumococcal disease may reduce the incidence of bacteremia in vaccinated patients with pneumonia.[161]

Exercise

All COPD patients can benefit from exercise training programs, which may improve muscle strength, exercise tolerance, dyspnea, and fatigue.[162] Referral to a formal pulmonary rehabilitation program can be helpful for most patients, but if this is unavailable, encourage patients to walk to a symptom-restricted maximum distance, rest, and then continue until a total of 20 minutes of exercise daily is achieved. Outdoor exercise should be avoided in areas of high air pollution or in temperature extremes.

Endurance exercise of the leg muscles is the main focus of exercise training, whether formal or informal, with walking, stationary cycling, and treadmill exercise commonly performed. High-intensity regimens are generally preferred, with initial targets of at least 60% of the maximum exercise tolerance, although lower-intensity exercise is also beneficial.[8] Exercise intensity is increased as tolerated and patients should exercise at least 3 times per week.[163] A resistance exercise component for the legs and arms may help in some activities of daily living and lessen the risk of falls. Bronchodilator therapy during exercise sessions may be helpful, as may supplemental oxygen.[8]

Nutrition

Weight loss and muscle wasting occur in 20–35% of patients with stable COPD, and can contribute to increased mortality and morbidity.[5] 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 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 of 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.[5,13] Combine nutritional

support with exercise wherever possible.[5] Referral to a nutritionist may be helpful if a patient is unable to maintain a healthy weight.

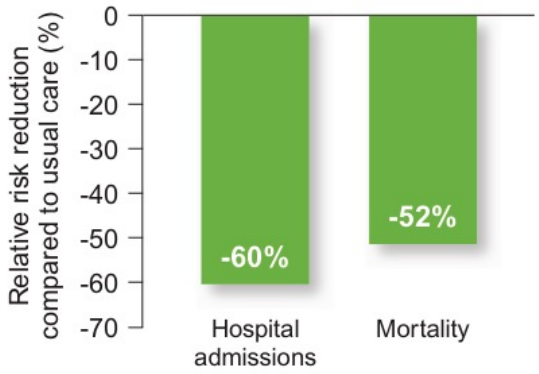
Pulmonary rehabilitation

Introduction

Pulmonary rehabilitation is a supervised exercise and strength training program where patients can also get education related to their disease or symptoms. Pulmonary rehabilitation does not directly improve lung function, but aims to optimize the function of other body systems to minimize the effect of lung dysfunction, improve exercise capacity, reduce dyspnea, and improve health-related quality of life.[85,13,163] Pulmonary rehabilitation programs can also reduce anxiety and depression, reduce the frequency of exacerbations and hospitalization, and possibly reduce mortality.[8]

A Cochrane review found that pulmonary rehabilitation improved exercise capacity and health-related quality of life as measured by the Chronic Respiratory Questionnaire for dyspnea, fatigue, emotional function, and "mastery."[164] Evidence for lower mortality and health care use is less clear, with studies reporting conflicting results. However, a meta-analysis of pulmonary rehab for patients after exacerbation found reduced hospital admissions over 25 weeks (pooled OR 0.22; 95% CI: 0.08 – 0.58; NNT=4) and mortality over 107 weeks (OR 0.28; 95% CI: 0.10 – 0.84; NNT=6), based on small studies of moderate methodologic quality.[165]

Figure 12: Pulmonary rehab reduces hospital admissions and mortality after an exacerbation[165]



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 these patients.[8] Home-based rehabilitation can be as effective as outpatient, hospital-based rehabilitation.[166] (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.[167]

Patient selection

Patients in pulmonary rehabilitation programs typically have severe disease (FEV_1/FVC <0.70, and FEV_1 <30-50% of predicted)[13] Those with less severe disease and significant exercise intolerance, however, may also benefit, as can those with severe subjective complaints of dyspnea without poor pulmonary function test values, and those for whom leg fatigue limits exercise tolerance.[8] Current GOLD guidelines recommend pulmonary rehabilitation for all COPD patients except GOLD A.[8] Pulmonary rehabilitation is not recommended for patients with unstable cardiac disease.[13]

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.[168]

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.[8]

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.[8]

Availability

Formal pulmonary rehabilitation programs are available for only a small number of patients who could benefit from this approach. Availability is particularly limited among lower-income, minority, and rural populations. The average cost for an 8-week program is about $2,200 per participant, and reimbursement from third-party payers varies regionally.[169] However, primary care physicians can prescribe several elements of a formal rehabilitation program based on the concepts above.

The 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.

Further information about both pulmonary rehabilitation and the American Thoracic Society statement are available at AlosaHealth.org/COPD.

Putting it all together: Non-pharmacological therapies at various stages of stable COPD

Table 9: Non-pharmacological therapies for COPD[8]

	GROUP A	GROUP B	GROUP C	GROUP D
Smoking cessation	✓	✓	✓	✓
Reduce occupational and environmental exposures	✓	✓	✓	✓
Exercise/physical therapy	✓	✓	✓	✓
Good nutrition	✓	✓	✓	✓
Vaccination	✓	✓	✓	✓
Pulmonary rehabilitation		✓	✓	✓
Pulmonologist referral			✓	✓
Address end-of-life decision making			✓	✓
Consider surgery in select patients				✓

Treating exacerbations

Exacerbations present challenges to COPD patients and their clinicians, and require strategies beyond maintenance therapy.[8] They tend to be infrequent early in the course of COPD and occur predominantly in moderate or severe disease.[170,171] Patients with advancing disease may have frequent exacerbations, defined as two or more.[8]

Exacerbations cause:[8]

- 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, fever, 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.[147]

Between 3% and 16% of exacerbations require hospitalization,[21,172] and in severe episodes, mortality can be as high as 10%.[35] Up to 25% of patients who require admission to an intensive care unit will die.[171] The prevention and treatment of exacerbations is thus a major objective of COPD management.[8]

Etiology

The main causes of COPD exacerbations include:[8]

- 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)

Exacerbations occur more frequently during winter.[8] Factors that increase the risk of severe exacerbations include increasing frequency of exacerbations, altered mental status, low BMI (20 kg/m2 or less), marked increase in symptoms or changes in vital signs, medical comorbidities, poor activity leavels, poor social support, severe baseline COPD, underutilization of home oxygen therapy and poor inhaler technique.[21,173,174] The cause of about one-third of severe exacerbations cannot be determined.[85]

Diagnosis

Early diagnosis and prompt management of exacerbations may prevent progressive functional deterioration and reduce hospital admissions.[85] The presenting symptom of increased dyspnea may be accompanied by increased cough and sputum, wheezing, chest tightness, change of sputum color, and fever. Non-specific symptoms such as malaise, insomnia, sleepiness, fatigue, depression, and confusion may occur.

The assessment of an exacerbation is based on functional status before the exacerbation, symptoms, and investigations such as lung function tests, arterial blood gas measurements, and 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 in the hospital.[85]

An increase in sputum volume and purulence (i.e., change in color) suggests a bacterial cause.[174] 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.[147] 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:[175]

- acute COPD exacerbation
- pneumonia
- pneumothorax
- pleural effusion
- lung cancer
- pulmonary embolus
- heart failure or an acute cardiac event
- arrhythmia

Hospitalization

Hospitalization may be necessary if any of the following are present:[8]

- 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 cope at home

Managing exacerbations

Bronchodilators

Increased airflow obstruction due to inflammation and bronchoconstriction is one of the primary events in COPD exacerbations. 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 (see also Appendix 2 for information on the use of inhaler devices).[113]

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.[8]

A 2014 Cochrane review found that short-term treatment of exacerbations with oral or parenteral corticosteroids:[176]

- 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

Although a 7 – 14-day course of a systemic glucocorticoid has been considered standard, the REDUCE trial comparing 40 mg prednisone daily for either 5 or 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.[177] A 2014 Cochrane review including this

study and others concluded that five days is likely sufficient.[178] In general, daily prednisone (30–50 mg) for exacerbations should not be continued longer than 14 days, as there is no advantage in prolonged therapy.[57] 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.[85] Such use confers a substantial risk of osteoporosis, cataract development, hyperglycemia, and other serious adverse effects.[147]

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.[8,177]

Antibiotics

Efficacy

The use of antibiotics in acute exacerbations of chronic bronchitis and COPD with increased cough and sputum purulence may reduce the risk of mortality by 77% and decrease the risk of treatment failure by 53%, according to a 2006 literature review, regardless of the specific antibiotic used.[179] The authors conclude however that these results should be interpreted with caution due to the differences in patient selection, antibiotic choice, small number of included trials and lack of control for interventions that influence outcome, such as use of systemic corticosteroids and ventilatory support. Nevertheless, this review supports antibiotics for patients with COPD exacerbations who have increased cough and sputum purulence and who are moderately or severely ill. Treatment of exacerbations with antibiotics in addition to oral corticosteroids may decrease the risk of both subsequent exacerbations and all-cause mortality.[180,181]

High quality evidence from a 2012 Cochrane review examining management of exacerbations, showed that antibiotics reduced the risk of treatment failure by a statistically significantly margin among inpatients with severe exacerbations (ICU patients not included) (RR 0.77; 95% CI: 0.65 – 0.91) regardless of the antibiotics used. Only one trial of ICU patients was reviewed; this trial of 93 patients showed a large and statistically significant effect in reducing the risk of treatment failure (RR 0.19; 95% CI: 0.08 – 0.45; high-quality evidence).[182]

Low-quality evidence from four trials in inpatients showed no effect of antibiotics on mortality, although high-quality evidence from one trial showed a significant benefit in ICU patients.[182]

The authors of the review concluded that antibiotics for COPD exacerbations showed large and consistent beneficial effects across outcomes of patients admitted to an ICU, but for outpatients and inpatients the results were inconsistent. The risk of treatment failure was significantly reduced in both inpatients and outpatients when all trials (1957 – 2012) were included but the effect size was smaller (and not quite statistically significant) when the analysis for outpatients was restricted to currently-used antibiotics. Also, antibiotics had no statistically significant effect on mortality and length of hospital stay among inpatients and almost no data on patient-reported outcomes exist.[182]

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.[8]

Choice of agent

The choice of antibiotic for exacerbations is controversial. Therapeutic decisions are often empiric, are based on the pathogens that are most common in these events, and are guided by any previous sputum cultures and/or local resistance patterns.[8] Many guidelines recommend a beta-lactam as first line therapy in primary care (amoxicillin or ampicillin) in combination with clavulanic acid.[8] In cases of penicillin allergy, alternatives include doxycycline, trimethoprim/sulfamethoxazole, cephalosporins, or an extended spectrum macrolide. Additional choices, particularly in more severely ill patients, include fluoroquinolones and parenteral third-generation cephalosporins and β-lactam / β-lactamase inhibitors.[183-185]

Duration of therapy

A response to antibiotic therapy is usually seen within 3-5 days; consider a change of antibiotic if response is unsatisfactory within this time. 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.[186] Most of the studies included in the meta-analysis were conducted in the community.[186]

Self-management

Patients at risk of a COPD exacerbation should be given advice that allows them to respond to such symptoms without delay.[31,57] Those able to self-manage should be encouraged to:

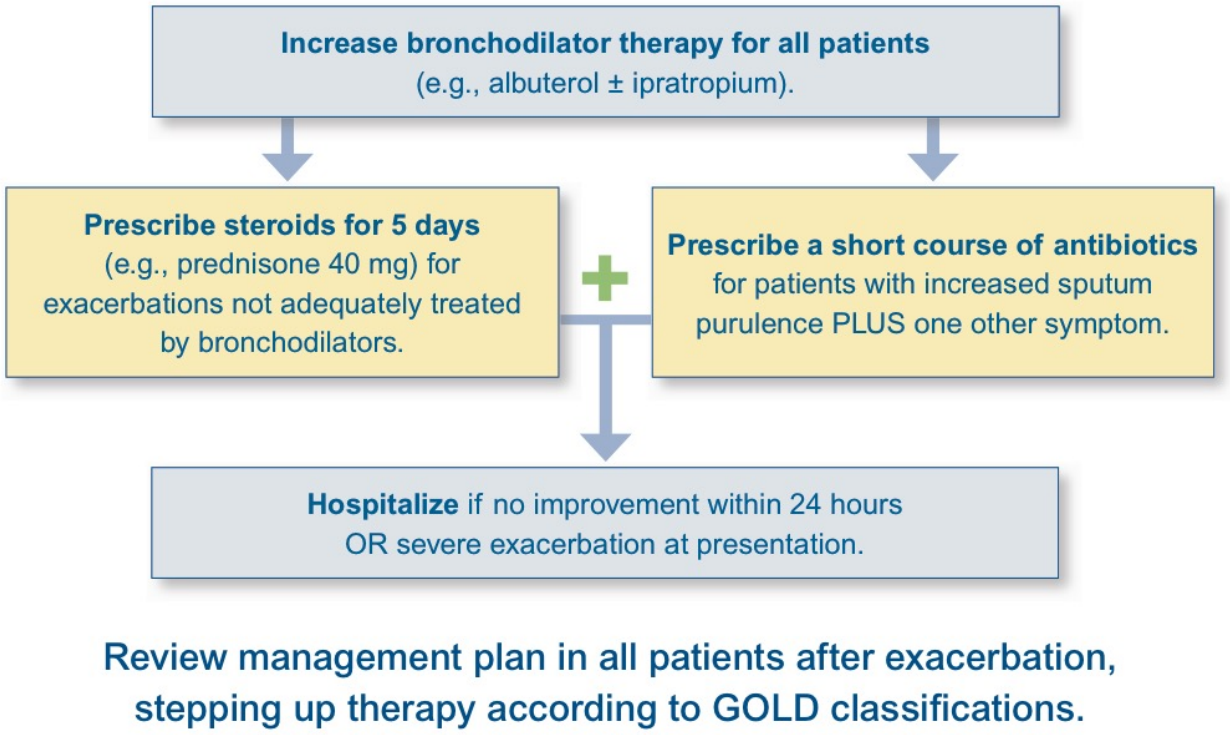
- Increase their bronchodilator therapy as appropriate to control their symptoms
- Start an oral corticosteroid if increased breathlessness interferes with activities of daily living
- Begin antibiotic therapy

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, ankle swelling, fever). The use of antibiotics and oral corticosteroids should be monitored.

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 (i.e., those with increased purulence or severe exacerbations). Appropriate patients can be educated about recognizing an exacerbation, initiating therapy at home, and seeking medical help if symptoms worsen despite additional therapy.

Putting it all together: Managing exacerbation in moderate to severe disease

Figure 13: Managing a COPD exacerbation in the outpatient setting[8]



Preventing acute exacerbations of COPD

Guidelines from the American College of Chest Physicians and the Canadian Thoracic Society recommend interventions to help prevent exacerbations.[187] These include standard measures such as influenza vaccination, use of inhalers, and smoking cessation, as well as pulmonary rehabilitation, and education and action plans with involvement of case management.

Readmission after a COPD exacerbation is common (~20%). Risk factors for readmission include reduced exercise, lack of prescriptions, comorbidities, and socioeconomic factors. Interventions to prevent readmission have shown inconsistent effects, with two studies showing a decrease in hospitalizations, but one US study showing increased mortality.[188] In addition, one study showed that many readmissions (~75%) after an exacerbation of COPD are not due to respiratory disease, reflecting the high prevalence of comorbid illness in this patient population.[189]

Systemic effects of COPD and co-morbid conditions

Sleep apnea

Evaluate excessive daytime sleepiness or sleep-disordered breathing in all COPD patients, especially the obese. This may require consideration of sleep studies, weight loss, reduced alcohol intake, and nocturnal CPAP. Excessive use of alcohol and sedatives exacerbates impaired gas exchange, predisposing to sleep-disordered breathing.

Gastro-Esophageal Reflux Disease (GERD)

GERD is a risk factor for COPD exacerbations.[190] Lifestyle changes, including stopping smoking, reduced intake of caffeine and alcohol, weight loss, exercise, and elevation of the head of the bed may help GERD symptoms. A therapeutic trial of an H_2-receptor antagonist or proton-pump inhibitor can clarify this diagnosis.

Osteoporosis

Patients with COPD often have below-normal bone mineral density (BMD) and an increased risk of fractures, because of smoking, corticosteroids, and decreased weight-bearing activity. Patients who take corticosteroids should undertake regular weight-bearing exercise if possible. Patients who have had long-term steroid therapy at lower doses and who have other risk factors should be screened for osteoporosis. Oral bisphosphonates are effective in preventing bone loss in men and women taking corticosteroids.[191]

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 heart failure with preserved ejection fraction (*cor pulmonale*). Oxygen therapy, calcium channel blockers, diuretics, digoxin, theophylline, endothelin receptor antagonists, phosphodiesterase-5 inhibitors, and anticoagulation therapy can be useful in the long-term management of pulmonary hypertension and *cor pulmonale*. The role of advanced pulmonary arterial vasodilator therapy in patients with COPD and intrinsic lung disease remains uncertain and specialist management is usually required.

Anxiety and depression

Anxiety and depression are common in COPD and should be assessed and treated.[22,192] These conditions may be exacerbated by medications such as theophylline and steroids.

Advanced disease

Referral for surgery

Surgical options for severe COPD are limited and pose significant risks, but may be appropriate for selected patients.[9] Lung volume reduction involves the removal of damaged tissue from one or both upper lobes, which may allow the lungs 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[193]

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. Several of these have demonstrated modest improvements in lung function, exercise tolerance, and symptoms. However, use of these procedures outside of clinical trials is currently not recommended.[8] 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.[194]

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.

Physicians, family members, and other healthcare workers 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, including palliative interventions such as morphine for sedation and for managing terminal dyspnea. Patients may choose to refuse life supportive care or have it withdrawn. Physicians 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 hospital, or in a nursing home.[8]

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:[195]

- 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

Here are some suggestions for talking about end-of-life care, prognosis, and advance care planning.[195]

Initiating discussions

- Frame the discussion as an important part of care for all patients with severe COPD.
- Identify whether the patient is unable 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.

Discussing advance care planning

- Frame as ‘‘hope for the best and prepare for the worst’’.
- If appropriate, clarify that advance care planning with a physician does not diminish a physician’s focus on maximizing the patient’s survival.
- Discuss the importance of advance directives if patients have strong views about the use of CPR, 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 all stages of COPD and individualized to the needs and preferences of the patient and family.[196] 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.[5]

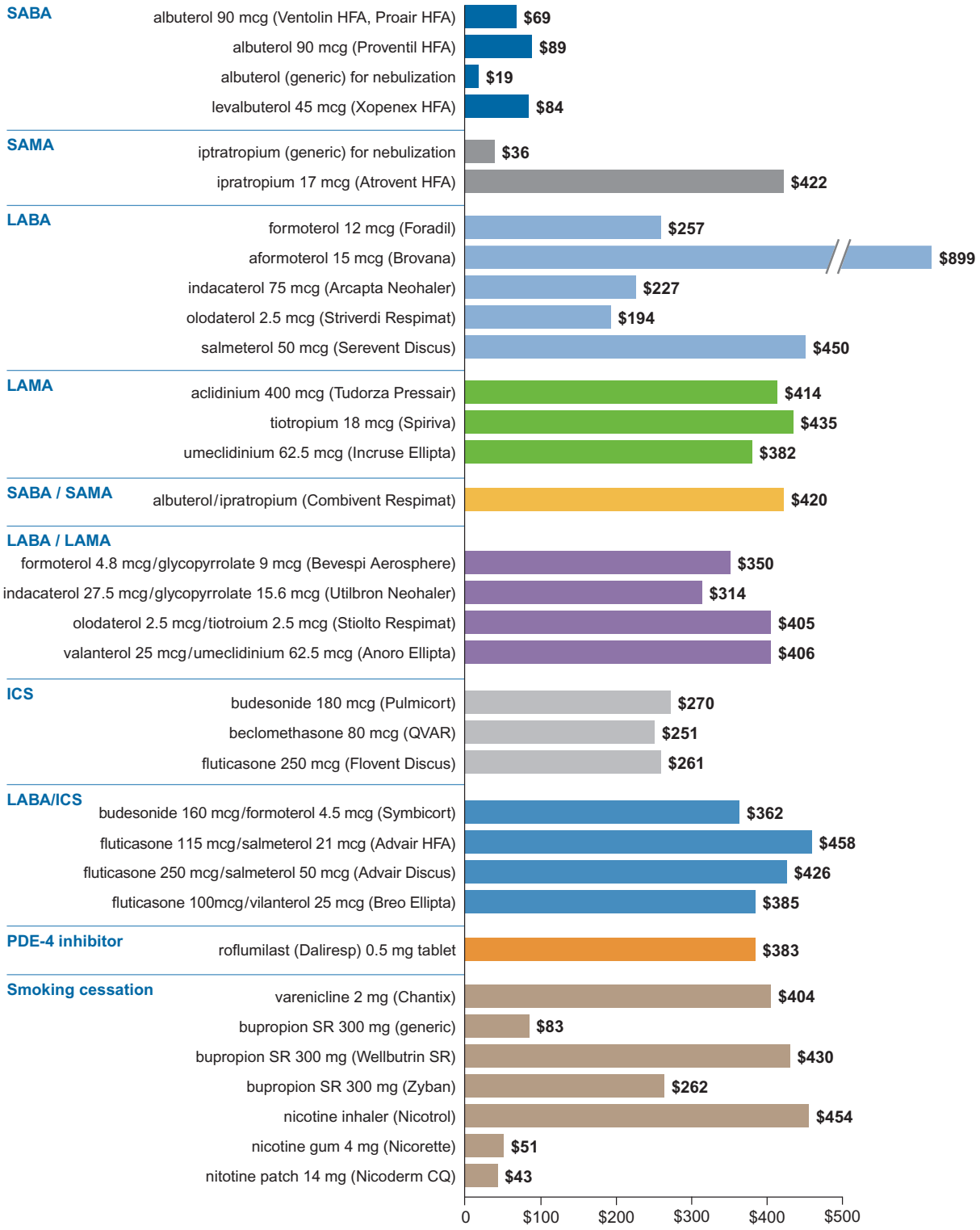
Patients with COPD may qualify for formal hospice services, which can provide excellent support and symptom control. Many episodes of worsening dyspnea in patients coming to the end of life can be avoided with appropriate hospice care.

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.

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 April 2017. For additional prices, visit goodrx.com or for formulary information, visit formularylookup.com or fingertipformulary.com.

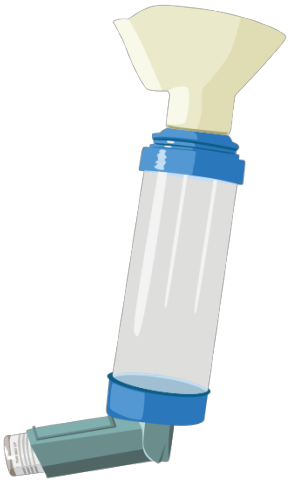
Appendix 1: COPD medications

Category	Type	Formulations	Brand names
Inhaled short-acting β-agonists (SABA)	Albuterol (also known as salbutamol)	MDI Nebulized solution	ProAir HFA Proventil HFA Ventolin Generic Accuneb
	Levalbuterol	MDI Nebulized solution	Xopenex Xopenex HFA
Inhaled long-acting β-agonists (LABA)	Salmeterol	DPI	Serevent Diskus
	Formoterol (also known as eformoterol)	DPI Nebulized solution	Foradil Aerolizer Perforomist
	Arformoterol	Nebulized solution	Brovana
	Indacaterol	DPI	Arcapta
	Olodaterol	MDI	Striverdi
Inhaled short-acting anticholinergics (SAMA)	Ipratropium	MDI Nebulized solution	Atrovent HFA Generic
Inhaled long-acting anticholinergics (LAMA)	Tiotropium	DPI	Spiriva
	Aclidinium	DPI	Tudorza
	Umeclidinium	DPI	Incruse
Inhaled corticosteroids (ICS)	Beclomethasone	MDI	Qvar
	Budesonide	DPI Nebulized solution	Pulmicort Flexhaler Pulmicort respules
	Fluticasone	MDI DPI Nebulized solution	Flovent Diskus Flovent HFA
Inhaled combination products SABA/SAMA	Albuterol/Ipratropium	MDI Nebulized solution	Combivent DuoNeb Generic
Inhaled combination products **LABA / ICS**	Budesonide/Formoterol	DPI	Symbicort
	Fluticasone/Salmeterol	MDI DPI	Advair HFA Advair Diskus
	Fluticasone/Vilanterol	DPI	Breo Ellipta

Appendix 1 (continued)

Category	Type	Formulations	Brand names
Inhaled combination products **LAMA / LABA**	Formoterol/Glycopyrrolate	MDI	Bevespi Aerosphere
	Indacaterol/Glycopyrronium	DPI	Utibron Neohaler
	Olodaterol/Tiotropium	MDI	Stiolto Respimat
	Vilanterol/Umeclidinium	DPI	Anoro Ellipta
Methylxanthines	Theophylline	Tablet Capsule Oral liquid	Generic Theo-24 (slow release) Elixophyllin Uniphyl
	Aminophylline (ethylenediamine salt of theophylline; 1 mg aminophylline is equivalent to 0.8 mg theophylline)	Oral Injection	Generic
Mucolytics	Acetylcysteine	Nebulized solution	Generic
Phosphodiesterase-4 inhibitors	Roflumilast	Tablet	Daliresp

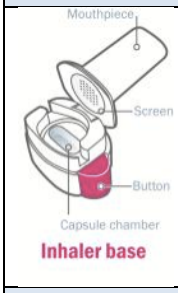
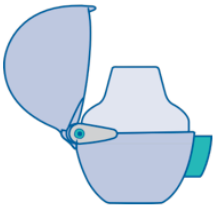
Appendix 2: Inhaler devices

Device	Considerations	Instructions for use
Metered Dose Inhaler (MDI)		
 e.g., Ventolin®, ProAir HFA®, Proventil HFA®, Xopenex HFA®, Atrovent HFA®, Qvar®, Flovent HFA®, Combivent®, Symbicort®, Advair HFA	Provides good delivery but requires good hand-breath coordination	If MDI is being used for the first time, or has not been used for one week or more, release one puff into the air before use Patients should breathe in slowly while actuating the MDI and then hold breath for 5 seconds If patient has difficulties, consider a spacer Educate patient on how to estimate quantity of medicine left in device Rinse mouth and throat after use of steroid-containing medication Inhaler should be cleaned at least once a week by wiping the inside and outside of the mouthpiece and the plastic casing with a dry cloth or tissue
MDI with Spacer		
	Reduces need for good hand-breath coordination Improves lung delivery of medicine Reduces oropharyngeal deposition and systemic absorption	Useful for patients with poor hand-breath coordination Spacers are easier to clean than nebulizers and are portable Large spacers are more effective than small spacers but bulkier to carry Educate patient to inhale medicine immediately to avoid deposition on the spacer walls Ensure one actuation of MDI into the space per inhalation Spacer should be washed with warm water and kitchen detergent at least once a month. Leave to dry by draining

Appendix 2 (continued)

Device	Considerations	Instructions for Use
Nebulizer		
 e.g. Perforomist®, Brovana®, Duoneb®	Drug delivery with a nebulizer is more expensive but no more effective than MDI with spacer	Use only for patients unable to use MDI with spacer Ensure patient can undertake the maintenance required
Respimat MDI		
	Provides good delivery with a low need for hand-breath coordination compared with other MDIs	Turn the clear base in the direction of the arrows until you hear a click. Flip open the cap. Breathe out slowly and fully. Before taking a breath in, bring the inhaler to your lips and close them around the mouth piece. Avoid covering the air vents. Take a slow, deep breath through your mouth and press the dose-release button. Continue to breathe in slowly for as long as you can. Hold your breath for 10 seconds, or as long as possible.
Dry Powder Inhaler (DPI)		
	Useful if unable to use MDI, but requires higher inspiratory flow rates than MDI and may not be appropriate in severe disease	Hold breath for at least 5 seconds after inhalation of medicine Rinse mouth and throat after use of steroid-containing medication Not as effective as MDI in exacerbations

Appendix 2 (continued)

Device	Considerations	Instructions for use
Turbuhaler		
 e.g., Pulmicort Flexhaler®		Hold device upright while priming Do not breathe into device or expose to moisture Dose counter or mark indicates remaining doses After use, wipe the turbuhaler with a clean dry tissue. The device must never get wet
Dry Powder Inhaler, DPI (continued)		
Accuhaler		
		Do not breathe into device or expose to moisture Dose counter or mark indicates remaining doses
Neohaler		
	Need to insert a capsule into the device	Counsel patient not to ingest the capsule Use inhaler immediately after loading a capsule Store separately from oral medication to avoid confusion Do not expose capsules to air or moisture
Handihaler		
	Need to insert a capsule into the device	Counsel patient not to ingest the capsule Use inhaler immediately after loading a capsule Store separately from oral medication to avoid confusion Do not expose capsules to air or moisture

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

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This material was produced by Michael H. Cho, M.D., M.P.H., Assistant Professor of Medicine; Michael A. Fischer, M.D., M.S., Associate Professor of Medicine (principal editor); Dae Kim, M.D., M.P.H., Sc.D., Assistant Professor of Medicine; Niteesh K. Choudhry, M.D., Ph.D., Professor of Medicine; Jerry Avorn, M.D., Professor of Medicine, all at Harvard Medical School; and Ellen Dancel, PharmD, M.P.H., Director of Clinical Materials Development at Alosa Health. Drs. Avorn, Cho, Choudhry, and Fischer are all physicians at the Brigham and Women's Hospital in Boston and Dr. Kim practices at the Beth Israel Deaconess Medical Center in Boston. None of the authors accepts any personal compensation from any drug company.

Medical writer: Stephen Braun.

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