

PHARMACY DRUG CLASS REVIEW

March 22, 2010

Disclaimer: Specific agents may have variations

COPD GUIDELINES

UPDATED DECEMBER 2009

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Highlights: The Quick-Read Information

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1. COPD is the 3rd leading cause of morbidity and mortality worldwide.
 - a. [True](#)
 - b. [False](#)
2. Which of the following is not a risk factor for COPD?
 - a. [Tobacco use](#)
 - b. [\$\alpha\$ -1 antitrypsin deficiency](#)
 - c. [Dust exposure](#)
 - d. [All of the above are risks](#)
3. Which of the following is not an extrapulmonary effect of COPD?
 - a. [Weight loss](#)
 - b. [Nutritional abnormalities](#)
 - c. [Cirrhosis](#)
 - d. [Skeletal muscle dysfunction](#)
4. With proper use of medications, COPD can be reversed and medications will no longer be warranted.
 - a. [True](#)
 - b. [False](#)
5. Regular use of long-acting beta-agonists is more effective and convenient than treatment with short-acting beta-agonists
 - a. [True](#)
 - b. [False](#)
6. Combining bronchodilators of different pharmacologic classes increases the risk of side effects versus increasing the dose or frequency of a single agent
 - a. [True](#)
 - b. [False](#)
7. Nonpharmacologic recommendations include all of the following, except:
 - a. [Supplemental O₂](#)
 - b. [Pulmonary rehabilitation](#)
 - c. [Surgery](#)
 - d. [Hyperbaric chamber](#)
8. Upon exacerbation, spirometry must be immediately performed to assess function
 - a. [True](#)
 - b. [False](#)

AGENTS IN THIS REVIEW:

β_2 -agonists:

Short-acting

Levalbuterol (Xopenex®)
Albuterol (ProAir®, Proventil®, Ventolin®)
Terbutaline (Brethine®)
Pirbuterol (Maxair)

Long-acting

Formoterol (Foradil®)
Arformoterol (Brovana®)
Salmeterol (Serevent®)

Anticholinergics

Short-acting

Ipratropium bromide (Atrovent®)

Long-acting

Tiotropium (Spiriva®)

Methylxanthines

Aminophylline
Theophylline (Theo-24®)

Glucocorticosteroids

Inhaled

Beclomethasone (QVAR®, Beconase AQ®)
Budesonide (Entocort®, Pulmicort®)
Fluticasone (Flovent®)
Triamcinolone (Azmacort®)

Systemic

Prednisone
Methylprednisolone (Medrol®)

Combinations

Short-acting β_2 -agonist/anticholinergic

Albuterol/Ipratropium (Combivent®)

Long-acting β_2 -agonist/glucocorticosteroid

Formoterol/Budesonide (Symbicort®)
Salmeterol/Fluticasone (Advair®)

FDA-approved COPD medications	Brand Name	Formulation	How Supplied	Duration of Action	IHA Tier
<i>β₂-agonists</i>					
<i>Short-acting</i>					
Albuterol	ProAir®	HFA	200 doses	4-6 hours	2
	Proventil®		200 doses		2
	Ventolin®		200 doses; dose counter		3
Levalbuterol	Xopenex®	Solution for nebulizer: 0.31mg/3ml, 0.63mg/3ml, 1.25mg/3ml; HFA	24 x 3ml doses; 200 doses	6-8 hours	3
Pirbuterol	Maxair®	Autohaler (MDI)	400 doses	4-6 hours	2
Terbutaline	Brethine®	Tablet	2.5mg, 5mg	4-6 hours	1*
<i>Long-acting</i>					
Arformoterol	Brovana®	Solution for nebulizer: 15mcg/2ml	30 x 2ml doses, 60 x 2ml doses	12+ hours	Non-formulary
Formoterol	Foradil®	Aerolizer (MDI)	60 capsules for aerolization	12+ hours	2*ST
Salmeterol	Serevent®	Diskus (MDI)	60 blisters for inhalation	12+ hours	2*ST
<i>Anticholinergics</i>					
<i>Short-acting</i>					
Ipratropium	Atrovent®	Solution for nebulizer: 0.5mg/2.5ml; HFA	25 x 2.5ml doses; 200 doses	6-8 hours	Nebulizer:1 HFA:2*
<i>Long-acting</i>					
Tiotropium	Spiriva®	Handihaler (MDI)	30 blisters for inhalation	24+ hours	2*O
<i>Methylxanthines</i>					
Aminophylline	Aminophylline	Tablet	100mg, 200mg	Variable; up to 24 hours	1*
Theophylline	Theo-24®	Capsules (extended-release)	100mg, 200mg, 300mg, 400mg	Variable; up to 24 hours	1*
<i>Glucocorticosteroids</i>					
<i>Inhaled</i>					
Beclomethasone	QVAR®	HFA: 40mcg, 80mcg/actuation	100 doses		1
Budesonide	Pulmicort®	Respules (solution for nebulizer): 0.25mg/2ml, 0.5mg/2ml, 1mg/2ml Flexhaler (MDI): 90mcg, 180mcg/actuation	30 x 2ml doses; 60 doses; 120 doses		Respules:1QL,A Flexhaler:1
Fluticasone	Flovent®	Diskus: 50mcg, 100mcg, 250mcg; HFA: 44mcg, 110mcg, 220mcg/actuation;	Diskus: 60 doses; HFA: 120 doses		Diskus:1 HFA:1*QL
Triamcinolone	Azmacort®	Discontinued as of 12/31/09			
<i>Systemic</i>					
Prednisone	Prednisone	Tablet	1mg, 2.5mg, 5mg, 10mg, 20mg, 25mg, 50mg		1
Methylprednisolone	Medrol®	Tablet	2mg, 4mg, 8mg, 16mg, 32mg		1
<i>Combinations</i>					
<i>Anticholinergic/ Short-acting β₂-agonist</i>					
Ipratropium/Albuterol	Combivent®	Solution for nebulizer: 0.5mg/3mg; MDI: 18mcg/103mcg per actuation	30 x 3ml doses; 200 doses		2QL
<i>Glucocorticosteroid/ Long-acting β₂-agonist</i>					
Budesonide/Formoterol	Symbicort®	MDI: 160mcg/4.5mcg, 80mcg/4.5mcg	120 doses		2*QL
Fluticasone/Salmeterol	Advair®	Diskus: 100mcg/50mcg, 250mcg/50mcg, 500mcg/50mcg; HFA: 45mcg/21mcg, 115mcg/21mcg, 230mcg/21mcg	Diskus: 60 doses; HFA: 120 doses		Diskus:2* HFA:2*QL

*: Maintenance medication; up to 90 day supply

QL: Quantity Limit; may be units/fill, fills/month or year, MDD, etc.

A: ≤ 8 years old only

ST: Step Therapy Program

O: ≥ 45 years old only

What's New in the 2009 Guidelines?

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Although most studies have indicated that existing COPD medications do not modify the long-term decline in lung function that accompanies the disease, limited evidence is showing that regular treatment with long-acting β_2 -agonists (LABAs), inhaled glucocorticosteroids, and the combination of the two can decrease the rate of decline of lung function.

In a large, long-term clinical trial it was found that the use of tiotropium (Spiriva®) in patients with COPD had no effect when added to other therapies on the rate of lung function decline but produced no evidence of cardiovascular risk.

In a large prospective clinical trial discussed in the previous guidelines, combination therapy of inhaled glucocorticosteroids and bronchodilators was found to increase the likelihood of pneumonia without a statistically significant increase in mortality. It has now been found that in those patients with FEV₁ less than 60%, pharmacotherapy with the combination decreased the rate of decline of lung function.

The use of endothelin-receptor antagonist bosentan is NOT recommended to treat patients with severe COPD, as it has failed to improve exercise capacity and may increase hypoxemia.

Nutritional supplements do NOT augment the effects of pulmonary rehabilitation in COPD patients.

Lung volume reduction surgery increases Pa(O₂) and decreases the use of supplemental oxygen during treadmill walking, as well as its self-reported use during rest, exertion and sleep for up to 24 months after surgery.

In patients with exacerbations severe enough to require hospitalization, pulmonary embolism should be ruled out; especially in patients at high risk for pulmonary embolism.

Budesonide alone (Pulmicort®), or in combination with formoterol (Symbicort®), are effective alternatives to oral glucocorticosteroids for treatment of exacerbations, although they are more expensive. This drug class is associated with a significant reduction of complications associated with exacerbations.

Updates to come in 2011 Guidelines:

Evidence will be reviewed with regard to:

Stages of COPD severity

The role of spirometric criteria, symptoms and medical history for COPD diagnosis

Treatment recommendations based on stage of severity

COPD and its comorbid conditions

Disease Overview

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Introduction

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease. It is not, however, curable. Although it is pulmonary in nature, it also comes with significant extrapulmonary effects. The pulmonary component is characterized by progressive airflow limitation that is associated with an exaggerated inflammatory response to noxious particles or gasses. Worldwide, cigarette smoking is the most encountered risk factor for COPD, however, air pollution from burning wood and biomass fuels is also seen to have a major impact in developing countries. Although this disease is not reversible, discontinuing exposure to noxious agents could potentially slow or halt disease progression.

Definitions

The working definition of COPD by the Global Initiative for Chronic Obstructive Lung Disease (GOLD):

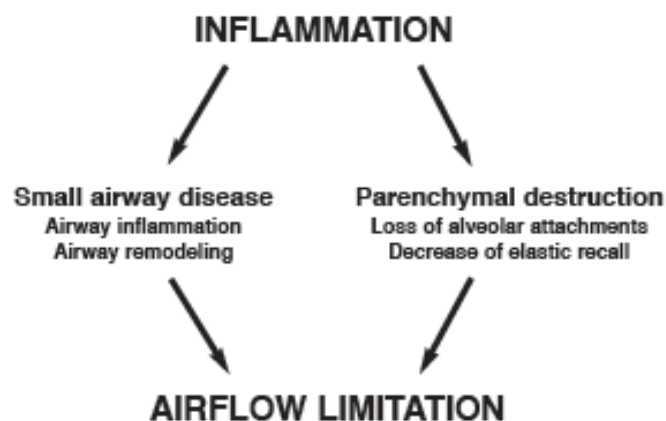
“Chronic Obstructive Pulmonary Disease is a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases.”

Many definitions of COPD have used emphysema and chronic bronchitis to describe the disease.

- **Emphysema** is a destruction of the gas-exchanging surfaces of lung which only describes one of several structural abnormalities is COPD.
- **Chronic bronchitis** is defined as the presence of a cough or sputum production for at least three months in each of two consecutive years. This is difficult to recognize because it often precedes airflow limitation in COPD or may not even occur at all.

Pathophysiology

- The chronic inflammation that accompanies COPD causes changes in structure of the airways leading to their narrowing.
- Changes can be found in proximal airways, peripheral vasculature, peripheral airways and lung parenchyma.
- In addition, the lung parenchyma is destroyed by inflammatory processes leading to the loss of alveolar attachments to the small airways.
- Lung elastic recoil is decreased as well, which diminishes the ability of airways to remain open during expiration.



Inflammation is further amplified by oxidative stress and an excess of proteases in the lung. Increased numbers of neutrophils can be found in the airway lumen, macrophages in the airway lumen, airway wall and parenchyma and CD8+ lymphocytes in the airway wall and parenchyma. Physiologic changes include mucus

hypersecretion, airflow limitation, air trapping, gas exchange abnormalities and cor pulmonale. Systemic features particularly seen in severe disease include cachexia, skeletal muscle wasting, increased cardiovascular disease risk, anemia, osteoporosis and depression.

Figure 4-1. Pathological Changes in COPD
<p>Proximal airways (trachea, bronchi > 2 mm internal diameter) <i>Inflammatory cells:</i> ↑Macrophages, ↑CD8⁺ (cytotoxic) T lymphocytes, few neutrophils or eosinophils <i>Structural changes:</i> ↑Goblet cells, enlarged submucosal glands (both leading to mucus hypersecretion), squamous metaplasia of epithelium⁹</p>
<p>Peripheral airways (bronchioles < 2mm i.d.) <i>Inflammatory cells:</i> ↑Macrophages, ↑T lymphocytes (CD8⁺ > CD4⁺), ↑B lymphocytes, lymphoid follicles, ↑fibroblasts, few neutrophils or eosinophils <i>Structural changes:</i> Airway wall thickening, peribronchial fibrosis, luminal inflammatory exudate, airway narrowing (obstructive bronchiolitis) Increased inflammatory response and exudate correlated with disease severity⁴</p>
<p>Lung parenchyma (respiratory bronchioles and alveoli) <i>Inflammatory cells:</i> ↑Macrophages, ↑CD8⁺ T lymphocytes <i>Structural changes:</i> Alveolar wall destruction, apoptosis of epithelial and endothelial cells⁵</p> <ul style="list-style-type: none"> • Centrilobular emphysema: dilatation and destruction of respiratory bronchioles; most commonly seen in smokers • Panacinar emphysema: destruction of alveolar sacs as well as respiratory bronchioles; most commonly seen in alpha-1 antitrypsin deficiency
<p>Pulmonary vasculature <i>Inflammatory cells:</i> ↑Macrophages, ↑T lymphocytes <i>Structural changes:</i> Thickening of intima, endothelial cell dysfunction, ↑ smooth muscle → pulmonary hypertension⁶.</p>

+Illustrations of many of the topics covered in this chapter can be found on the GOLD Website: <http://www.goldcopd.org>.

Comorbidities

- Extrapulmonary effects of COPD include weight loss, nutritional abnormalities and skeletal muscle dysfunction.
- Patients are also at an increased risk of myocardial infarction, angina, osteoporosis, respiratory infection, bone fracture, depression, diabetes, sleep disorders, anemia, glaucoma and possibly lung cancer, although this could be due to the common risk factor of cigarette smoking.
- Once developed, COPD and its comorbidities cannot be cured. As such, treatment will be continuous for the remainder of a patient's life.

Risk Factors

While cigarette smoking is the most prevalent risk factor for COPD development, there are several others that may play a role. Genetically, individuals with a severe hereditary deficiency of alpha-1 antitrypsin may find themselves more susceptible to COPD development. Occupational dusts and chemicals, such as vapors, irritants and fumes have been shown to be capable of causing COPD. Indoor air pollution, such as the burning of biomass fuels in confined spaces, is associated with an increased COPD risk in developing countries, especially among women. In addition, factors related to lung growth and development and oxidative stress, as well as gender, age, history of respiratory infections, prior tuberculosis infection, socioeconomic status, nutrition or comorbidities may render an individual at increased risk of COPD contracture.

Burden

COPD is the leading cause of morbidity and mortality **worldwide**. It is directly related to the prevalence of tobacco smoking, although in some countries air pollution plays a role as well. COPD's prevalence is expected to increase in the future. In the United States, it is presently the 4th leading cause of death behind heart disease, cancer and stroke.²

Stages of COPD

The stages of COPD are typically classified by spirometry. This device is essential for diagnosis as it is the most widely available, reproducible test of lung function. It is administered after use of a bronchodilator and provides a description of pathological changes. FEV₁, or forced expiratory volume in one second, is a value of interest from spirometry to quantify the patient's present lung function. FVC is the forced vital capacity, or the volume of air that can forcibly be blown out after a full inspiration. FEV₁/FVC is a ratio that is typically from 0.75 to 0.8 in healthy adults. This ratio is often less than 0.7 in patients with COPD because the FEV₁ is reduced due to airway limitation and the FVC may be increased due to airtrapping.

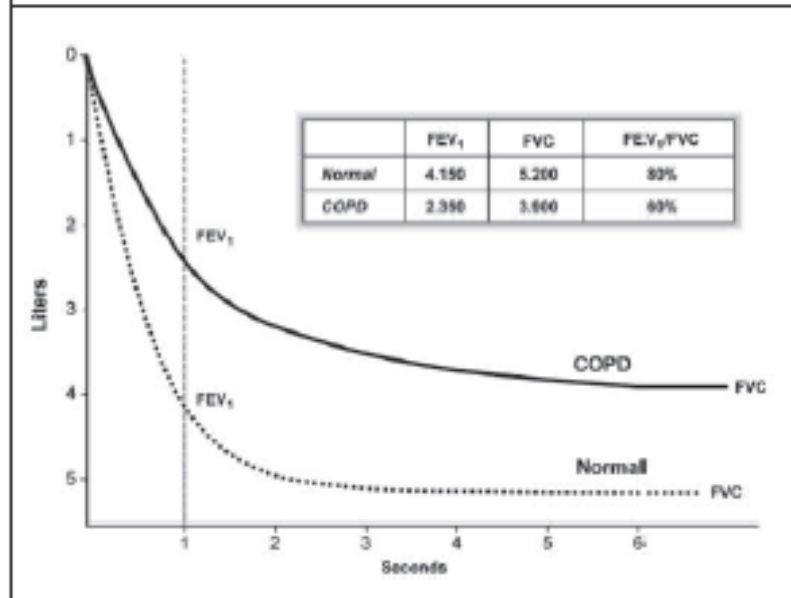
At stage I, or mild COPD, the patient is usually unaware that lung function is abnormal although chronic cough or sputum may be present. A patient at stage II, or moderate COPD, may begin to develop shortness of breath on exertion. This is the stage that medical attention is often sought due to chronic respiratory symptoms or an exacerbation. Stage III, or severe COPD, often comes at a great impact to the patient's quality of life due to greater shortness of breath, reduced exercise capacity, fatigue and repeated exacerbations. Stage IV, or very severe COPD, is indicative of respiratory failure. It may lead to effects on the heart such as cor pulmonale, which can be identified clinically as elevation of jugular venous pressure and pitting ankle edema. At this point, quality of life is severely impaired and exacerbations may be life threatening.

Stages of COPD	Airflow Limitation	FEV ₁ /FVC	FEV ₁	Characteristics
<i>Stage I (mild)</i>	Mild airflow limitation	<0.70	≥80% predicted	Symptoms of chronic cough and sputum production may be present.
<i>Stage II (moderate)</i>	Worsening airflow limitation	<0.70	50-79% predicted	Shortness of breath on exertion; cough and sputum production; patient typically seeks medical attention
<i>Stage III (severe)</i>	Further worsening airflow limitation	<0.70	30-49% predicted	Greater shortness of breath, reduced exercise capacity, fatigue and repeated exacerbations
<i>Stage IV (very severe)</i>	Severe airflow limitation	<0.70	<30% predicted OR <50% predicted plus chronic respiratory failure	Quality of life severely impaired and all exacerbations life threatening

Diagnosis

Spirometry is the gold standard for diagnosing COPD and monitoring its progression. It should be performed in any individual that it is thought to be exhibiting signs and symptoms of COPD. Symptoms of concern include dyspnea that is progressive, worse with exercise, persistent and described by the patient as labored or gasping, a chronic cough which may be intermittent or unproductive, chronic sputum production or history of tobacco smoking or exposure to occupational dusts or chemicals or smoke from home cooking or heating fuels. Even with these signs and symptoms present, a diagnosis can only be made using spirometry.

Figure 5.1-5. Normal Spirogram and Spirogram Typical of Patients with Mild to Moderate COPD*



*Postbronchodilator FEV₁ is recommended for the diagnosis and assessment of severity of COPD.

Pharmacotherapy

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Drug Therapy

As COPD is not curable, the goal of pharmacologic treatment in COPD is to prevent or control symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance. Once diagnosed, patients with COPD will take medications continuously for the remainder of their lives. While most studies indicate that the existing medications do not alter the long-term decline in lung function in this disease, limited evidence has suggested that regular treatment with long-acting beta-agonists and/or glucocorticosteroids could decrease the rate of decline of lung function (**new to guidelines 2009**).

In addition to COPD being a progressive disease, its treatment is also progressive. Treatment tends to be cumulative, as more medications are added as the disease worsens. Regular treatment must be maintained at the same level for long periods of time unless significant side effects occur or the disease worsens. Because individuals differ, careful monitoring is required. At each office visit, medication dosages, frequency of use, adherence, technique and effectiveness should be assessed and evaluated.

Therapy by Stage	Stage I	Stage II	Stage III	Stage IV
<i>Active reduction of risk factors</i>	X	X	X	X
<i>Influenza vaccination</i>	X	X	X	X
<i>Short-acting bronchodilator</i>	X	X	X	X
<i>Long-acting bronchodilator(s)</i>		X	X	X
<i>Inhaled glucocorticosteroids (if repeated exacerbations)</i>			X	X
<i>Long-term oxygen (if chronic respiratory failure)</i>				X
<i>Consideration of surgical treatments</i>				X

Bronchodilators

Bronchodilators are central to symptomatic management of COPD. They are able to widen airways by affecting smooth muscle tone. This provides an improvement in spirometry as it allows for increased expiration. This drug class, however, **does NOT improve lung elastic recoil**. Bronchodilators can improve the emptying of the

lungs and reduce dynamic hyperinflation at rest and during exercise. They are available as both long and short acting formulations. Bronchodilators are often formulated in inhalers so it is essential that the patient's technique be reassessed at each visit. If the patient is elderly or having difficulty, spacer devices and breath activated devices are available. Some bronchodilators have solutions to be used with a nebulizer, but the guidelines do not recommend these for regular treatment because they are expensive and require more maintenance. Adverse effects of bronchodilators are pharmacologically predictable and dose dependent. Those side effects generated from inhaled treatment are less likely and resolve more quickly than with oral treatment. A combination of bronchodilators from different classes improves efficacy and decreases the risk of side effects when compared to increasing the dose of a single bronchodilator.

Bronchodilators: β_2 -agonists

β_2 -agonists relax airway smooth muscle by stimulating β_2 -adrenergic receptors, which increases cyclic AMP and produces functional antagonism to bronchoconstriction. Oral therapy is slower in onset and has more side effects than inhaled treatment. Short-acting beta-agonists (SABAs) are often termed "rescue inhalers" and are given on an as-needed basis for symptomatic relief and on a regular basis to prevent or reduce symptoms. When taken, they can exert their effect within 20 minutes and wear off within 4 to 6 hours. Long-acting beta-agonists (LABAs) are to be used on a regular basis to combat airway inflammation. They are known to last for at least 12 hours and regular treatment is more effective and convenient than treatment with SABAs. It should be noted that formoterol and salmeterol carry a black box warning for monotherapy in asthma patients. This black box warning does not apply to patients using the drugs for COPD.

Side effects with this drug class can occur and are due to stimulation of β_2 -adrenergic receptors which can produce resting sinus tachycardia and could even potentially precipitate cardiac rhythm disturbances in those very susceptible patients. Exaggerated tremor is possible in older patients being treated with high doses of β_2 -agonists and would necessitate a dose decrease to a tolerated level.

FDA-approved COPD medications	Brand Name	Formulation	How Supplied	Duration of Action	IHA Tier
β_2-agonists					
<i>Short-acting</i>					
Albuterol	ProAir®	HFA	200 doses	4-6 hours	2
	Proventil®		200 doses		2
	Ventolin®		200 doses; dose counter		3
Levalbuterol	Xopenex®	Solution for nebulizer: 0.31mg/3ml, 0.63mg/3ml, 1.25mg/3ml; HFA	24 x 3ml doses; 200 doses	6-8 hours	3
Pirbuterol	Maxair®	Autohaler (MDI)	400 doses	4-6 hours	2
Terbutaline	Brethine®	Tablet	2.5mg, 5mg	4-6 hours	1*
<i>Long-acting</i>					
Arformoterol	Brovana®	Solution for nebulizer: 15mcg/2ml	30 x 2ml doses, 60 x 2ml doses	12+ hours	Non-formulary
Formoterol	Foradil®	Aerolizer (MDI)	60 capsules for aerolization	12+ hours	2*ST
Salmeterol	Serevent®	Diskus (MDI)	60 blisters for inhalation	12+ hours	2*ST
Combinations					
<i>Anticholinergic/ Short-acting β_2-agonist</i>					
Ipratropium/Albuterol	Combivent®	Solution for nebulizer: 0.5mg/3mg; MDI: 18mcg/103mcg per actuation	30 x 3ml doses; 200 doses		2QL
<i>Glucocorticosteroid/ Long-acting β_2-agonist</i>					
Budesonide/Formoterol	Symbicort®	MDI: 160mcg/4.5mcg, 80mcg/4.5mcg	120 doses		2*QL
Fluticasone/ Salmeterol	Advair®	Diskus: 100mcg/50mcg, 250mcg/50mcg, 500mcg/50mcg; HFA: 45mcg/21mcg, 115mcg/21mcg, 230mcg/21mcg	Diskus: 60 doses; HFA: 120 doses		Diskus:2* HFA:2*QL

*: Maintenance medication; up to 90 day supply
 QL: Quantity Limit; may be units/fill, fills/month or year, MDD, etc.

ST: Step Therapy Program

Bronchodilators: Anticholinergics

Anticholinergics exert their effects through blockage of acetylcholine's effect on M3 receptors. Short-acting anticholinergics also block M2 receptors. This class lasts for 6 to 8 hours, which is longer than SABAs. Long-acting anticholinergics are selective for M3 and M1 receptors and have effect for over 24 hours.

Side effects seen with anticholinergics are typically systemic due to their poor absorption. The main side effect is dryness of the mouth, but there have been reports of bitter, metallic taste and prostatic symptoms as well. Lastly, nebulizer solutions used with masks have been reported to precipitate acute glaucoma.

FDA-approved COPD medications	Brand Name	Formulation	How Supplied	Duration of Action	IHA Tier
Anticholinergics					
<i>Short-acting</i>					
Ipratropium	Atrovent®	Solution for nebulizer: 0.5mg/2.5ml; HFA	25 x 2.5ml doses; 200 doses	6-8 hours	Nebulizer:1 HFA:2*
<i>Long-acting</i>					
Tiotropium	Spiriva®	Handihaler (MDI)	30 blisters for inhalation	24+ hours	2*O
Combinations					
<i>Anticholinergic/ Short-acting β_2-agonist</i>					
Ipratropium/Albuterol	Combivent®	Solution for nebulizer: 0.5mg/3mg; MDI: 18mcg/103mcg per actuation	30 x 3ml doses; 200 doses		2QL

*: Maintenance medication; up to 90 day supply
 O: \geq 45 years old only
 QL: Quantity Limit; may be units/fill, fills/month or year, MDD, etc.

Bronchodilators: Methylxanthines

There is controversy surrounding the methylxanthine drug class because their exact effect is unknown. It is thought that they may act as non-selective phosphodiesterase inhibitors, but they have also been reported to have a range of non-bronchodilator actions. Data is presently lacking on the duration of action of methylxanthines in COPD. Although changes in inspiratory muscle function have been reported in patients using theophylline, it is unknown whether this reflects changes in dynamic lung volumes or a primary effect on the muscle. Theophylline is effective in COPD but the guidelines note that due to its potential toxicity, inhaled bronchodilators are preferred when available. It is noted that low doses of theophylline reduce COPD exacerbation but do NOT increase post-bronchodilator lung function.

Adverse effects are a significant consideration with methylxanthines. **Toxicity is dose related and the largest problem is the small therapeutic window. Often, benefit isn't seen until a near-toxic dose is given.** Methylxanthines are nonspecific in their inhibition leading to a wide range of effects, including atrial and ventricular arrhythmias, grand mal convulsions, headaches, insomnia, nausea and heartburn. **Unlike other bronchodilators, methylxanthines come with the risk of overdose.**

FDA-approved COPD medications	Brand Name	Formulation	How Supplied	Duration of Action	IHA Tier
Methylxanthines					
Aminophylline	Aminophylline	Tablet	100mg, 200mg	Variable; up to 24 hours	1*
Theophylline	Theo-24®	Capsules (extended-release)	100mg, 200mg, 300mg, 400mg	Variable; up to 24 hours	1*

*: Maintenance medication; up to 90 day supply

Combination Therapy

Although monotherapy with LABAs appears to be safe, combining bronchodilators from different pharmacologic classes with different durations and mechanisms of action may increase the degree of bronchodilation achieved with equivalent or lesser side effects. For example, a combination of a SABA and an anticholinergic produces greater and more sustained improvements in FEV1 than either drug alone and does not produce evidence of tachyphylaxis. In a study comparing salmeterol/fluticasone and tiotropium, there was no difference in the number of exacerbations; however, more individuals in the combination group completed the study. The combination of a β_2 -agonist, an anticholinergic and/or theophylline may produce even further improvements in lung function.

FDA-approved COPD medications	Brand Name	Formulation	How Supplied	Duration of Action	IHA Tier
Combinations					
<i>Anticholinergic/ Short-acting β_2-agonist</i>					
Ipratropium/Albuterol	Combivent®	Solution for nebulizer: 0.5mg/3mg; MDI: 18mcg/103mcg per actuation	30 x 3ml doses; 200 doses		2QL
<i>Glucocorticosteroid/ Long-acting β_2-agonist</i>					
Budesonide/Formoterol	Symbicort®	MDI: 160mcg/4.5mcg, 80mcg/4.5mcg	120 doses		2*QL
Fluticasone/ Salmeterol	Advair®	Diskus: 100mcg/50mcg, 250mcg/50mcg, 500mcg/50mcg; HFA: 45mcg/21mcg, 115mcg/21mcg, 230mcg/21mcg	Diskus: 60 doses; HFA: 120 doses		Diskus:2* HFA:2*QL

*: Maintenance medication; up to 90 day supply

QL: Quantity Limit; may be units/fill, fills/month or year, MDD

Glucocorticosteroids

The effects of glucocorticosteroids in COPD are much less dramatic than in asthma. In management of stable COPD, this class has a limited role and is restricted to certain indications. In management of exacerbations, however, this class is effective and commonly deployed. Glucocorticosteroids shorten recovery time and improve lung function, while decreasing length of hospital stay and poor outcomes of early relapse and treatment failure. Oral glucocorticosteroids are typically used in this instance due to cost effectiveness, but inhaled glucocorticosteroids are also effective.

Inhaled glucocorticosteroids

Regular treatment with inhaled glucocorticosteroids has been shown to reduce the frequency of exacerbations in Stage III and IV patients. Treatment with this class is recommended by the guidelines in patients with more advanced disease with repeated exacerbations. The dose-response relationships and long-term safety of this class in COPD is not yet known. Long-term **HIGH-dose** studies have shown a slight INCREASED incidence of skin bruising and variable effects on bone density.

FDA-approved COPD medications	Brand Name	Formulation	How Supplied	Duration of Action	IHA Tier
Glucocorticosteroids					
<i>Inhaled</i>					
Beclomethasone	QVAR®	HFA: 40mcg, 80mcg/actuation	100 doses		1
Budesonide	Pulmicort®	Respules (solution for nebulizer): 0.25mg/2ml, 0.5mg/2ml, 1mg/2ml Flexhaler (MDI): 90mcg, 180mcg/actuation	30 x 2ml doses; 60 doses; 120 doses		Respules:1QL,A Flexhaler:1
Fluticasone	Flovent®	Diskus: 50mcg, 100mcg, 250mcg; HFA: 44mcg,	Diskus: 60 doses; HFA: 120 doses		Diskus:1 HFA:1*QL

		110mcg, 220mcg/actuation;		
Triamcinolone	Azmacort®	Discontinued as of 12/31/09		
Combinations				
<i>Glucocorticosteroid/ Long-acting β_2-agonist</i>				
Budesonide/Formoterol	Symbicort®	MDI: 160mcg/4.5mcg, 80mcg/4.5mcg	120 doses	2*QL
Fluticasone/ Salmeterol	Advair®	Diskus: 100mcg/50mcg, 250mcg/50mcg, 500mcg/50mcg; HFA: 45mcg/21mcg, 115mcg/21mcg, 230mcg/21mcg	Diskus: 60 doses; HFA: 120 doses	Diskus:2* HFA:2*QL

*: Maintenance medication; up to 90 day supply

A: \leq 8 years old only

QL: Quantity Limit; may be units/fill, fills/month or year, MDD, etc.

Oral glucocorticosteroids

Existing COPD guidelines have recommended utilization of a short course (two weeks) of oral glucocorticosteroids to identify COPD patients who might benefit from use of long-term oral or inhaled glucocorticosteroids. This trial is based on evidence that short-term effects predict long-term effects of oral glucocorticosteroids on FEV₁ and evidence that patients with asthma don't necessarily respond to an inhaled bronchodilator acutely, but do show significant bronchodilation after a short course of oral glucocorticosteroids. More evidence is beginning to show that a short course of glucocorticosteroids is a poor predictor of long term response and therefore, a short-term trial of oral glucocorticosteroids cannot be recommended in patients in Stage II, III or IV and poor response to a bronchodilator.

Long-term use of **ORAL** glucocorticosteroids on FEV₁ has been analyzed with **NO** clear evidence of benefit. Side effects are apparent with this course, however, such as steroid myopathy which contributes to muscle weakness, decreased functionality and respiratory failure in subjects with advanced COPD. It is for these reasons that long-term oral glucocorticosteroids are not recommended as treatment for COPD.

FDA-approved COPD medications	Brand Name	Formulation	How Supplied	Duration of Action	IHA Tier
Glucocorticosteroids					
<i>Systemic</i>					
Prednisone	Prednisone	Tablet	1mg, 2.5mg, 5mg, 10mg, 20mg, 25mg, 50mg		1
Methylprednisolone	Medrol®	Tablet	2mg, 4mg, 8mg, 16mg, 32mg		1

Combination glucocorticosteroids

An inhaled glucocorticosteroid in combination with a LABA is more effective than each drug individually in reducing exacerbations and improving lung function. In patients with an FEV₁ less than 60%, combination of an inhaled glucocorticosteroid and a LABA **decreased the rate of lung function decline (new to guidelines 2009).**

FDA-approved COPD medications	Brand Name	Formulation	How Supplied	Duration of Action	IHA Tier
Combinations					
<i>Glucocorticosteroid/ Long-acting β_2-agonist</i>					
Budesonide/Formoterol	Symbicort®	MDI: 160mcg/4.5mcg, 80mcg/4.5mcg	120 doses		2*QL
Fluticasone/ Salmeterol	Advair®	Diskus: 100mcg/50mcg, 250mcg/50mcg, 500mcg/50mcg; HFA: 45mcg/21mcg, 115mcg/21mcg, 230mcg/21mcg	Diskus: 60 doses; HFA: 120 doses		Diskus:2* HFA:2*QL

*: Maintenance medication; up to 90 day supply

QL: Quantity Limit; may be units/fill, fills/month or year, MDD, etc.

Other Pharmacologic Treatments

Vaccines

Influenza vaccines can reduce serious illness and death in COPD patients. Pneumococcal polysaccharide vaccine is recommended for COPD patients 65 years and older.

Alpha-1 antitrypsin therapy

Those young patients with established emphysema and severe hereditary alpha-1 antitrypsin deficiency may be candidates for alpha-1 augmentation therapy. This therapy is very expensive and **NOT** recommended for COPD patients unless their disease is related to alpha-1 antitrypsin deficiency.

Antibiotics

There is **NO** evidence that prophylactic, continuous use of antibiotics is effective in decreasing COPD exacerbations. Debate still ongoing.

Mucolytic agents

The regular use of mucolytic agents in COPD has been evaluated in several studies with controversial results. While some patients may benefit from use of this drug class, the benefit is thought to be **minimal** and is thus NOT recommended at this point.

- There IS evidence that in patients not yet treated with inhaled glucocorticosteroids, treatment with mucolytic agents MAY reduce exacerbations.

Antioxidant agents

After speculation in a few small studies, N-acetyl-cysteine was investigated in a large randomized controlled trial which showed that it had **NO** effect on the frequency of exacerbations, ...

- Except in those patients that had not yet been treated with inhaled glucocorticosteroids.

Immunoregulators

Initial studies show that use of an immunoregulator in patients with COPD decreases the severity and frequency of exacerbations. Additional long-term studies, however, will be needed to examine this finding further before its recommendation.

Antitussives

Although cough may be present, regular use of antitussives in stable COPD patients is NOT recommended.

Vasodilators

Inhaled nitric oxide and other agents were investigated for their vasodilatory effects, as belief that pulmonary hypertension in COPD is associated with a poorer prognosis.

- Results, however, showed **NO** effect and inhaled nitric oxide was shown to **worsen** gas exchange therefore making it contraindicated.

Narcotics

Opioids are effective for treating dyspnea in patients with advanced COPD but there is insufficient data whether nebulized opioids are effective.

Others

Nedocromil and leukotriene modifiers have not yet been adequately tested in COPD patients. There is **NO** evidence of benefit and some evidence of HARM from an anti-TNF-alpha antibody tested in moderate to severe COPD. Endothelin-receptor antagonist bosentan **failed** to improve exercise capacity and may increase hypoxemia (new to guidelines in 2009).

Non-pharmacologic Treatment

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Rehabilitation

Pulmonary rehabilitation is used to reduce COPD symptomatology, improve quality of life and increase participation in everyday activities. In order to accomplish the goals of pulmonary rehabilitation, it is essential to address non-pulmonary problems caused by COPD, such as exercise deconditioning, relative social isolation, altered mood states, muscle wasting and weight loss. Several trials have been performed to investigate the impact of pulmonary rehabilitation and on average, rehabilitation increases peak workload by 18%, peak oxygen consumption by 11% and endurance time by 87% of baseline. These findings correlate to a 49 meter improvement in six-minute walking distance. Although benefit will wane after the rehabilitation program ends, if exercise training is maintained at home the patient's health status will remain improved from pre-rehabilitation levels. The minimum length of effective rehabilitation programs is 6 weeks and the longer the program continues, the more effective the results. Unfortunately, no program has been able to maintain its benefits over time. In addition to exercise training and education, nutrition counseling is an important part of rehabilitation. About a quarter of COPD patients experience a reduction in their BMI and fat free mass. These patients may become breathless while eating and should be advised to take small, frequent meals. Improvement of nutritional state is important in these patients, as it can lead to improved respiratory muscle strength.

Oxygen Therapy

Oxygen therapy is the principal nonpharmacologic treatment in Stage IV COPD patients. Oxygen can be given continuously, during exercise or to relieve acute dyspnea. The primary goal of this therapy is to increase baseline PaO₂ to at least 8.0 kPa and/or produce an SaO₂ at least 90%, which is sufficient to ensure adequate delivery of oxygen to vital organs and preserve their function.

A decision to use long-term oxygen continuous administration of oxygen (>15 hours per day) is based on waking PaO₂ values. It is generally given to Stage IV patients who have PaO₂ ≤7.3 kPa or SaO₂ ≤88% or <8.0kPa or SaO₂ of 88% if there is evidence of pulmonary hypertension, peripheral edema suggesting congestive cardiac failure, or polycythemia (hematocrit >55%).

Surgical Treatments

A bullectomy is a surgical procedure for bullous emphysema. In this surgery, a large bulla that does not contribute to gas exchange is removed which decompresses the adjacent lung parenchyma.. This surgery can be performed thoracoscopically and has been shown to be effective in reducing dyspnea and improving lung function in carefully selected patients. When considering the benefit of the surgery in a particular patient, it is appropriate to estimate the effect of the bulla on the lung and the function of the nonbullous lung. A thoracic CT scan, arterial blood gas measurement and respiratory tests are essential before making any decisions about a patient having resection surgery. Normal or minimally reduced diffusing capacity, absence of significant hypoxemia and evidence of regional reduction in perfusion with good perfusion in the remaining lung are indications a patient will benefit from the surgery.

Lung volume reduction surgery (LVRS) is a procedure that removes parts of the lungs to reduce hyperinflation. This would make a patient's respiratory muscles more mechanically efficient and increase the elastic recoil pressure of the lung which would thus improve expiratory flow rate. A large trial showed that LVRS patients had improvements in maximal work capacity and quality of life, increased time to first exacerbation and reduced frequency of exacerbations.

Lung transplantation is a consideration in patients with very advanced COPD. The potential for this procedure is limited by the shortage of donor organs, which has led some centers to adopt single-lung transplants. This

procedure is not without complications, with the potential for operative mortality, acute rejection, infection, lymphoproliferative disease and lymphomas.

Exacerbation Management

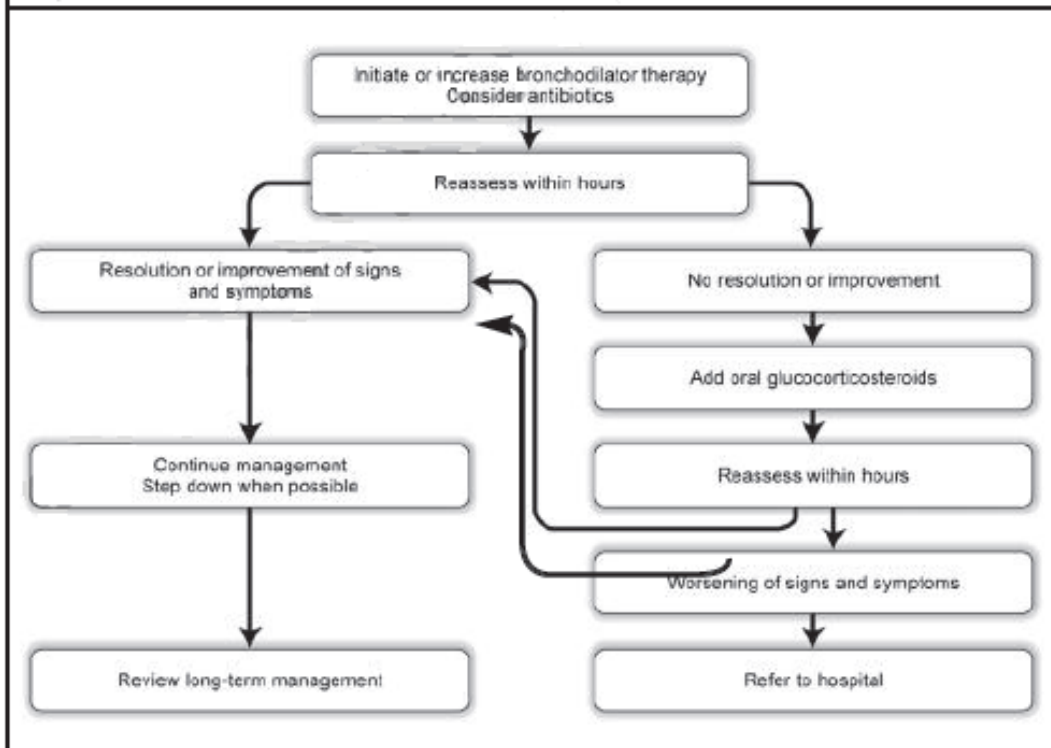
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An exacerbation of COPD is defined as “an event in the natural course of the disease characterized by a change in the patient’s baseline dyspnea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD.” Patients typically present with increased breathlessness and often wheezing and chest tightness, increased cough and sputum, a change in the appearance of sputum, and fever. Nonspecific complaints such as tachycardia, tachypnea, malaise, insomnia, sleepiness, fatigue, depression and confusion may also be present during exacerbations. The most common causes of exacerbations are air pollution and an infection of the tracheobronchial tree. During an acute exacerbation, spirometry is difficult to perform and is therefore not recommended. Pulse oximetry and arterial blood gas measurement can be effectively used to assess the need for supplemental oxygen. Chest X-rays and electrocardiograms are used to rule out differential diagnoses that could mimic the symptoms of acute exacerbation. Whole blood count can be used to identify polycythemia or bleeding. Antibiotic treatment can be given empirically in the present of purulent sputum during an exacerbation. Biochemical tests can be assessed for abnormalities commonly seen with COPD such as electrolyte disturbance, poor glucose control or metabolic acidosis.

A pulmonary embolism should be considered in patients requiring hospitalization from severe exacerbation (**new to guidelines 2009**). In the 10 to 30% of patients that do not respond to treatment during apparent exacerbation, it is important to reevaluate the patient for other conditions including pneumonia, congestive heart failure, pneumothorax, pleural effusion, pulmonary embolism and cardiac arrhythmia. If the acute dyspnea is thought to be secondary to congestive heart failure, serum levels of brain-type natriuretic peptide would be elevated and can be assessed.

Figure 5.4-2. Algorithm for the Management of an Exacerbation of COPD at Home (adapted from ref³⁴⁶)

The exact criteria for home vs. hospital treatment remain uncertain and will vary by health care setting. If it is determined that care can be initiated at home, this algorithm provides a stepwise therapeutic approach.



After an exacerbation not requiring hospitalization, the dose and/or frequency of existing short-acting bronchodilator therapy, preferably a SABA, is increased. If the patient is not already using an anticholinergic medication, it can be added until the symptoms improve. Glucocorticosteroids given systemically are effective in exacerbation management. They shorten recovery time, improve lung function and hypoxemia and may reduce the risk of early relapse, treatment failure and length of hospital stay. Glucocorticosteroids should be considered for addition to bronchodilators if the patient's baseline FEV₁ is <50% predicted. Oral prednisolone is preferable, dosed as 30-40mg daily for 7-10 days. Budesonide alone (Pulmicort®), or in combination with formoterol (Symbicort®), are also effective alternatives, albeit more expensive (**new to guidelines 2009**). The use of antibiotics is common after exacerbations when the cause is believed to be an infection.

If the patient presents to the emergency department during an exacerbation, their symptoms, blood gases and chest X-ray will be assessed and they will initially receive supplemental oxygen. If the exacerbation is thought to be potentially life threatening, they will be sent to the intensive care unit immediately; otherwise they will continue to receive treatment in the emergency department. After receiving oxygen for 30 to 60 minutes, blood gases will be reevaluated. Bronchodilators will be increased in dose or frequency, and if a prompt response to a SABA does not occur, β_2 -agonists will often be combined with anticholinergics, spacers or nebulizers will be used and intravenous methylxanthines will be considered. Glucocorticosteroids will be added, either orally or intravenously, and antibiotics will be used if the patient is experiencing increased dyspnea, increased sputum volume and purulence. Mechanical ventilation is another option to consider.

Summary

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Stages of COPD	Airflow Limitation	FEV₁	Characteristics	Pharmacotherapy
<i>Stage I (mild)</i>	Mild airflow limitation	≥80% predicted	Symptoms of chronic cough and sputum production may be present.	Short-acting bronchodilator
<i>Stage II (moderate)</i>	Worsening airflow limitation	50-79% predicted	Shortness of breath on exertion; cough and sputum production; patient typically seeks medical attention	Add: Long-acting bronchodilator
<i>Stage III (severe)</i>	Further worsening airflow limitation	30-49% predicted	Greater shortness of breath, reduced exercise capacity, fatigue and repeated exacerbations	Add: Inhaled glucocorticosteroid
<i>Stage IV (very severe)</i>	Severe airflow limitation	<30% predicted OR <50% predicted plus chronic respiratory failure	Quality of life severely impaired and all exacerbations life threatening	Add: Oxygen supplementation

[Wrong answer: try again or read on.](#)

References

1. Global Initiative for Chronic Obstructive Lung Disease: Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (Updated December 2009). 2009 Medical Communications Resources, Inc. 1-109.
2. Centers for Disease Control and Prevention. Leading Causes of Death (Data are for the U.S.). Last updated: Dec 31, 2009. Accessed: Mar 8, 2010. << <http://www.cdc.gov/nchs/fastats/lcod.htm>>>

Quiz Answers

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1. B
2. D
3. C
4. B
5. A
6. B
7. D
8. B