Medication Therapy Management of Chronic Obstructive Pulmonary Disease
Overview and Epidemiology of Chronic Obstructive Pulmonary Disease (COPD)
COPD

• COPD is a chronic disease characterized by airflow limitation that is not fully reversible
• This airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases

Chronic obstructive pulmonary disease is characterized by airflow limitation that's not fully reversible. The airflow limitation in COPD is typically progressive and it’s associated with an abnormal inflammatory response of the lungs to noxious particles or gases.
COPD: The Forgotten Disease

• For more than a decade, COPD has been largely ignored because clinicians felt that there was nothing that could be done.

• With new knowledge and new therapies, there is renewed interest about the prevention and management of COPD.

Switching to some COPD statistics, in the United States nearly 11 million people have a physician diagnosis of COPD, but the impact of the disease is felt to be much higher in that in various surveys nearly 24 million people report having impaired lung function as measured by spirometry. COPD is a leading cause of death in the United States, currently representing the fourth leading cause of death. In 2002, over 120,000 deaths in the United States were attributed to COPD. And since the turn of the century, female death rate from COPD has exceeded that of males.
This slide summarizes the growth in death rate from COPD that's been observed over the last 20 years and the more rapid death rate growth seen in females compared to males.
Epidemiology

- COPD is a leading cause of morbidity and mortality worldwide, and results in an economic and social burden that is both substantial and increasing.

- Prevalence and morbidity data greatly underestimate the total burden of COPD because the disease is usually not diagnosed until it is clinically apparent and moderately advanced.
The economic cost of COPD is very significant as well. In this case, you can see the direct cost and the indirect cost are fairly equal.
Medication Management and Related Services for the COPD Patient

- Tobacco cessation counseling and risk factor avoidance
- Immunizations
- Recommendation and selection of medication and device products
- Education about proper use of medication
- Monitoring for safety and efficacy of therapy
- Considering therapeutic alternatives and cost
Medication Management and Related Services for the COPD Patient (continued)

• Monitoring co-morbidities and potential interactions
• Provision and monitoring of oxygen therapy
• Provision of home care equipment and supplies
• Referral to other community services and resources
COPD Etiology

- 80% to 90% of COPD is attributed to a current or past history of cigarette smoking
- Other causes/factors include:
  - Air pollution
  - Exposure to secondary cigarette smoke
  - History of serious respiratory infections during childhood
  - Genetics (including Alpha-1 antitrypsin (AAT) deficiency)
  - Occupational exposures

The primary causative factor of COPD is a current or past history of cigarette smoking. Other causes include exposure to environmental pollutants as might occur during air pollution or due to occupational exposures, exposure to secondhand tobacco smoke, a history of serious respiratory infections during childhood. There’s also a rare inherited disorder, called α1-antitrypsin deficiency, which can result in emphysema.
COPD Phenotypes

• **Chronic bronchitis**
  – Chronic inflammation present in bronchial tubes, increased mucus production, and productive cough
  – Common features: chronic cough with mucus production, shortness of breath, and recurrent infections

• **Emphysema**
  – Destruction of alveoli units resulting in decreased gas exchange
  – Common features: cough, shortness of breath, and decreased exercise tolerance

COPD is commonly broken down into two major phenotypes or two presentations of the disease. Patients with chronic bronchitis typically have chronic inflammation in the airway, increased mucus production, and a chronic cough. These patients have a cough during several months of the year, and their main complaints are shortness of breath and they suffer from recurrent infections of the airway.

The other major type is emphysema. In emphysema there’s destruction of the alveolar units of the airway resulting in decreased gas exchange. Patients with emphysema chronically complain of a cough, although it’s typically nonproductive. They also complain of shortness of breath and reduced exercise tolerance.
Chronic exposure to noxious particles and gases that are present in tobacco smoke or in the environment result in inflammation in COPD. This chronic inflammation results in an increase in oxidative stress and in the activity of various proteinases that are present in the airway. These two processes result in the damage that characterizes COPD.
Although inflammation also plays a role in COPD, the nature of the inflammation differs from that seen in asthma. The most common cause of COPD is an exposure to tobacco smoke. As I’ve summarized on this slide: components of tobacco smoke stimulate an inflammatory reaction involving various cells in the airway of patients with COPD, and ultimately resulting in parenchymal destruction or loss of lung tissue.
The consequences of airflow limitation that occurs in COPD is that patients end up with gas trapping and hyperinflated lungs. As a result, those patients suffer frequent exacerbations, and exacerbations lead to chronic symptoms of shortness of breath or dyspnea. These symptoms result in decreased activity and overall decreased exercise tolerance and the resultant disability that goes along with having COPD.
Diagnosis of COPD

- Diagnosis of COPD should be considered in any patient who has the following:
  - Symptoms of cough
  - Sputum production
  - Dyspnea
  - History of exposure to risk factors for the disease

- Spirometry should be obtained in all persons with the following history:
  - Exposure to cigarettes and/or environmental or occupational pollutants
  - Family history of chronic respiratory illness
  - Presence of cough, sputum production or dyspnea
This graph demonstrates spirometry results for normal patients as well as patients with asthma and COPD. The top line represents spirometry from a normal patient.

After taking a maximal inhalation, a patient is instructed to blow out as hard and fast as possible. In the normal situation, the majority of air that leaves the lung comes out within the first second and then the remainder of the air leaves the lung over the next several seconds.

In a patient with COPD, as demonstrated on the bottom line, both the rate of airflow out of the lung and the total amount of air that leaves the lung is actually reduced.

In a patient with asthma, as is depicted in the middle two lines, before treatment of asthma the rate of airflow out the lung is decreased and actually looks similar to a patient with COPD. Because the airflow obstruction in asthma is largely reversible after treatment with a bronchodilator, the rate of airflow out of the lung approaches that of a normal person.
## Biologic Features

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<th><strong>Asthma</strong></th>
<th><strong>COPD</strong></th>
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<td><strong>Cellular infiltration</strong></td>
<td>Eosinophils</td>
<td>Neutrophils</td>
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<td>CD4+ T(_h)2 lymphocytes</td>
<td>Macrophages</td>
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<td>Activation of mast cells</td>
<td>CD8+ lymphocytes</td>
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<td><strong>Mediators</strong></td>
<td>LTD(_4)</td>
<td>LTB(_4)</td>
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<td>IL-4, IL-5</td>
<td>IL-8</td>
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<td>TNF-alpha</td>
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<td><strong>Structural consequences</strong></td>
<td>Fragile epithelium</td>
<td>Squamous metaplasia of epithelium</td>
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<td></td>
<td>Thickened basement membrane</td>
<td>Parenchymal destruction</td>
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<td>Mucous metaplasia</td>
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<td>Glandular enlargement</td>
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### Clinical Features

<table>
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<tr>
<th></th>
<th><strong>Asthma</strong></th>
<th><strong>COPD</strong></th>
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</table>
| **History & presentation** | Early onset (<40 years)  
Varying or intermittent symptoms  
Night-time symptoms  
Presence of allergy, rhinitis, eczema or combination of these  
Family history | Midlife onset  
Slowly progressive symptoms  
Prominent smoking history |
| **Physiologic**      | Airflow limitation - largely reversible  
Airway hyperresponsiveness - significant | Airflow limitation - largely irreversible  
Airway hyperresponsiveness - variable |

Mucous
The American Thoracic Society and the GOLD Guidelines also provide a severity classification for patients with COPD. COPD is categorized based on spirometry results; the primary result being the predicted FEV₁. This ranges from patients with mild COPD, or patients who are at risk for COPD who have fairly normal FEV₁’s at greater than or equal to 80%. Patients who have FEV₁’s of less than 80% are categorized as having COPD ranging in severity from moderate to very severe disease.
Patient Characteristics

- At Risk: experiences morning cough
- Stage 1: no limitation, but symptoms with exercise
- Stage 2: activities are limited, symptoms more chronic
- Stage 3: patient is restricted in what they can do; dyspnea is chronic; frequent exacerbations
- Stage 4: ‘bed to chair’ existence; end of life planning appropriate
From a patient’s perspective, you can see the impact that COPD has on their activities in daily living and some normal activities that patients might participate in, again, ranging from mild to severe disease.
Factors Determining Severity Of Chronic COPD

- Severity of symptoms, including dyspnea
- Severity of airflow limitation
- Frequency and severity of exacerbations
- Presence of complications of COPD
- Presence of respiratory insufficiency
- Co-morbidity
- General health status (including nutrition)
  - Low BMI (<21) associated with poor outcomes
- Number of medications taken
COPD Exacerbations Impact on Lung Function


Infrequent exacerbators (n = 16)
FEV₁ change = 32 ml/year

Frequent exacerbators (n = 16)
FEV₁ change = 40 ml/year

COPD Exacerbations: Survival

8.3% mortality
1st admission

Follow-up days
n = 205 patients

Impact of Exacerbations on COPD Mortality

• Following hospitalization for a COPD exacerbation, mortality rates are
  – 22 to 43% after 1 year
  – 36 to 49% after two years
• Factors associated with higher mortality
  – Increasing age
  – Higher partial carbon dioxide ($pCO_2$)
  – Chronic prednisone therapy
  – Reduced health status and co-morbidities
Management Strategies for COPD
Available Guidelines for COPD

ATS/ERS

GOLD

NICE

CTS

Objectives of COPD Management

- Prevent disease progression
- Relieve symptoms
- Improve exercise tolerance
- Improve health status
- Prevent and treat exacerbations
- Prevent and treat complications
- Reduce mortality
- Minimize side effects from treatment
Components of COPD Management

• Patient education
• Assess and monitor disease
• Reduce risk factors
• Manage stable COPD
• Manage exacerbations
### Treatment Strategies Based on Severity

<table>
<thead>
<tr>
<th>New (2003)</th>
<th>0: At Risk</th>
<th>I: Mild</th>
<th>II: Moderate</th>
<th>III: Severe</th>
<th>IV: Very Severe</th>
</tr>
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<tbody>
<tr>
<td>Characteristics</td>
<td>• Chronic Symptoms • Exposure to risk factors • Normal spirometry</td>
<td>• FEV1/FVC &lt; 70% • FEV1 &lt; 80% • With or without symptoms</td>
<td>• FEV1/FVC &lt; 70% • 57% ≤ FEV1 &lt; 80% • With or without symptoms</td>
<td>• FEV1/FVC &lt; 70% • 30% ≤ FEV1 &lt; 50% • With or without symptoms</td>
<td>• FEV1/FVC &lt; 70% • FEV1 &lt; 30% or FEV1 &lt; 50% predicted plus chronic respiratory failure</td>
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<td>Avoidance of risk factor(s): influenza vaccination</td>
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<tr>
<td><strong>Add</strong> short-acting bronchodilator when needed</td>
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<td><strong>Add</strong> regular treatment with one or more long-acting bronchodilators</td>
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<td><strong>Add</strong> rehabilitation</td>
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<tr>
<td><strong>Add</strong> inhaled glucocorticosteroids if repeated exacerbations</td>
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<tr>
<td><strong>Add</strong> long-term oxygen if chronic respiratory failure</td>
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<tr>
<td>Consider surgical treatments</td>
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Patient Education

- Causes and natural course of COPD
- Recognizing signs and symptoms
- Avoiding exposure to risk factors
- Role and proper use of medications
- Inhalation techniques
- Pulmonary rehabilitation
- Supplemental oxygen therapy
- Recognizing exacerbations
- End of life decisions
Chronic Management Of COPD
(GOLD Guidelines Am J Respir Crit Care Med 2001;163:1256-1276)

- Diagnose
  - Education
    ✓ Spirometry

- Reduce Risk
  - Education
    ✓ Smoking cessation
    ✓ Immunize
    ✓ Reduce other exposures

- Reduce Symptoms
  - Education
    ✓ Bronchodilators
    ✓ Consider inhaled steroids
    ✓ Pulmonary rehabilitation

- Reduce Complications
  - Education
    ✓ Consider oxygen
    ✓ Treat exacerbations
Reduce Risk Factors:
Key Points

• Reducing exposure to tobacco smoke, occupational dusts, and chemicals, and indoor and outdoor air pollutants

• Smoking cessation is the single most effective -- and cost-effective -- intervention to reduce the risk of developing COPD and stop its progression
Reduce Risk Factors:
Key Points

• Brief tobacco dependence treatment is effective and every tobacco user should be offered at least this treatment at every visit

• Three types of counseling are especially effective: practical counseling, social support as part of treatment, and social support arranged outside of treatment
In women severe obstruction associated with accelerated decline.
The 5 As for Tobacco Cessation

- Ask about tobacco use.
- Advise tobacco users to quit.
- Assess readiness to make a quit attempt.
- Assist with the quit attempt.
- Arrange follow-up care.

As a final review, the 5 A’s are as follows:

- **Ask** about tobacco use.
- **Advise** tobacco users to quit.
- **Assess** readiness to make a quit attempt.
- **Assist** with the quit attempt.
- **Arrange** follow-up care.

Each of these is a key component of comprehensive tobacco cessation counseling interventions.
For patients who are not ready to quit, clinicians can deliver tailored, motivational messages by applying the 5 R’s:

**Relevance:** Encourage the patient to indicate why quitting is personally relevant. Be as specific as possible. Motivational information has the most impact if it is relevant to the patient’s disease status or risk, family or social situation (e.g., having children in the home), health concerns, age, sex, and other important patient characteristics (e.g., prior quitting experience, personal barriers to cessation).

**Risks:** Ask the patient to identify consequences of tobacco use. Suggest and highlight those that seem most relevant to the patient and emphasize that other forms of tobacco (such as smokeless, or lower-tar-level cigarettes) will not eliminate the risks. Risks of tobacco use are discussed in the *Epidemiology of Tobacco Use* and *Pathophysiology of Tobacco-Related Disease* modules.

**Rewards:** Ask the patient to identify benefits of quitting. Highlight those that seem relevant to the patient. Examples of benefits of cessation are discussed in the *Epidemiology of Tobacco Use* module.

**Roadblocks:** Ask the patient to identify barriers to quitting and potential methods for circumventing each barrier. Suggest and highlight those that seem most relevant to the patient. Common barriers include withdrawal symptoms, fear of failure, weight gain, lack of support, depression, and enjoyment of tobacco.

**Repetition:** Repeat the motivational intervention whenever possible. Tobacco users who have failed in previous quit attempts should be reminded that most people make repeated quit attempts before they are successful.
Decades of research tell us that clinicians can have an important impact on their patients’ likelihood of achieving cessation. A meta-analysis of 29 studies determined that patients who received a tobacco cessation intervention from a nonphysician clinician or a physician clinician were 1.7 and 2.2 times as likely to quit (at 5 or more months postcessation), respectively, compared with patients who did not receive such an intervention (Fiore et al., 2000). Self-help materials were only slightly better than no clinician.

The clinician and patient should discuss and develop effective cognitive and behavioral coping strategies for handling specific situations in which a person will be tempted to use tobacco.

Research shows that using both cognitive and behavioral strategies increases a patient’s likelihood of quitting (Prochaska & DiClemente, 1992). These strategies are described in the next few slides.

**Note to instructor(s):** Have students refer to the *Coping with Quitting: Cognitive and Behavioral Strategies* handout. This handout provides specific examples of coping strategies for various situations.
Reduce Risk Factors: Key Points

- There are effective pharmacotherapies for tobacco dependence
- Add medications to counseling if necessary
- Progression of many occupationally induced respiratory disorders can be reduced or controlled by reducing inhaled particles and gases
**Note to instructor(s):** Throughout this module, Rx and OTC are used to indicate prescription and over-the-counter (nonprescription) products, respectively.

This slide shows the years when the different pharmacologic agents for smoking cessation received FDA approval:

- In 1984, the nicotine gum (Nicorette) was the first nicotine replacement product to be approved by the FDA.
- In 1991, prescription transdermal nicotine patches became available.
- In 1996, Nicorette gum, Nicoderm CQ patches, and Nicotrol patches (no longer available) became available without a prescription; the prescription nicotine nasal spray (Nicotrol NS) was approved the same year.
- Bupropion SR (Zyban) was approved in 1997 as the only nonnicotine product to be used as an aid for smoking cessation. The nicotine inhalation system (Nicotrol inhaler) also received FDA approval for prescription use in 1997.
- The most recent nicotine replacement product to be approved by the FDA is the nicotine lozenge (Commit). This product was approved for nonprescription use in 2002.
- In 2006, a new class of medications is introduced with the FDA approval of varenicline (Chantix).
Few head-to-head trials have compared the various tobacco cessation therapies. In a randomized controlled trial comparing the four NRT formulations available at the time, the products performed similarly, but patient compliance was higher with the patch, followed by the gum, which was higher than the inhaler and nasal spray (Hajek et al., 1999).

This bar chart summarizes the long-term (≥6-month) quit rates observed with the different NRT products, bupropion SR and varenicline (Gonzales et al., 2006; Hughes et al., 2004; Jorenby et al., 2006; Silagy et al., 2004). These data derive from 124 different placebo-controlled trials; therefore, it is inappropriate to compare the active medications with respect to clinical efficacy. What this chart does illustrate, however, is that the quit rates from each of the methods is approximately twice that of its corresponding placebo control treatment arm.

Each of the pharmacotherapy options depicted in the chart is considered effective. When patients ask for assistance with their quit attempt, any product can be recommended, if not contraindicated. However, when assisting patients in choosing a product, clinicians should consider additional factors. The number of cigarettes smoked per day (or time to first cigarette, for the nicotine lozenge), level of dependence, advantages and disadvantages of each product, methods used for prior quit attempts and reasons for relapse, and the patient's own product preference need to be considered. Behavioral counseling should be used in conjunction with all pharmacologic therapies.

Influenza Vaccination in Elderly Patients with COPD

- Influenza vaccination associated with
  - Fewer hospitalizations for pneumonia and influenza (ARR = 0.48)
  - Lower risk of death (ARR = 0.30)

ARR = Adjusted Risk Ratio


*For pneumonia or influenza. ARR = adjusted risk ratio.

• From Adrienne-Advanced COPD, slide 32
• Harvey-influenza vaccination
Medications for COPD

- Short-acting, inhaled beta$_2$ agonists
  - Albuterol, pirbuterol, levalbuterol
- Inhaled anticholinergics (short and long-acting)
  - Ipratropium, tiotropium
- Long-acting, inhaled beta$_2$ agonists
  - Formoterol, salmeterol, arformoterol
- Theophylline
- Inhaled or systemic corticosteroids
- Combination LABA/ICS
Manage Stable COPD

- Stepwise increase in treatment based on disease severity
- Health education can play a role in improving skills, ability to cope with illness, and health status. It is effective in accomplishing certain goals, including smoking cessation
- None of the existing medications for COPD affects long-term decline in lung function that is the hallmark of this disease
- Pharmacotherapy for COPD is used to decrease symptoms and/or complications
Monitoring Outcomes from COPD Therapy

- Improve lung function
- Reduce symptoms, including dyspnea
- Reduce complications
  - exacerbation frequency and severity
  - Reduce hospitalizations
- Improve quality of life
- Avoid side effects from medications
Route of Delivery for Inhalation Therapies

- Method of delivery of inhalation therapy varies among settings
- Clinical studies suggest equal efficacy between nebulization and Metered dose inhaler (MDI) (with holding chamber)
- Dry powder inhaler (DPI) administration difficult in acute setting
This algorithm, defined according to the GOLD Guidelines, talks about a rational approach to patients with COPD, starting at the top with very mild disease and progressing through the most extensive disease. For patients at risk for COPD, one of the first interventions is tobacco cessation and making sure the patient receives appropriate immunization. At Stage I, patients still experience very intermittent symptoms and could be controlled with short-acting bronchodilator therapy. But as we progress to more extensive COPD, combinations of bronchodilators or bronchodilators combined with inhaled corticosteroids are often required.
Bronchodilators in Stable COPD

- Bronchodilator medications are central to symptom management in COPD.

- Inhaled therapy is preferred.

- The choice between bronchodilators or combination therapy depends on availability and individual response in terms of symptom relief and side effects.
Bronchodilators in Stable COPD

- Bronchodilators are prescribed on an as needed or on a regular basis to prevent or reduce symptoms.
- Regular treatment with long-acting inhaled bronchodilators is more effective and convenient than treatment with short-acting bronchodilators, but more expensive.
- Combining bronchodilators may improve efficacy and decrease the risk of side effects compared to increasing the dose of a single bronchodilator.
Rapid-acting Bronchodilators

- No evidence for substantial advantage of one class over another
  - Short-acting beta agonists (SABAs) onset is 5 min; peak within 15 to 30
  - Anticholinergic agents onset is 15 min; peak in 30 to 60
- Primary considerations
  - Efficacy of individual agents
  - Efficacy of combinations
  - Route of administration
- Many rapid-acting bronchodilators are also short-acting
β₂-Agonists

- Primary action: bronchodilation due to relaxation of bronchial smooth muscle by stimulating action at adrenergic receptor
- Classified as short-acting (albuterol, levalbuterol, pirbuterol) or long-acting (formoterol, salmeterol)
- Short-acting β₂-agonists are the primary rescue therapy used by patients with asthma or COPD
- Common side effects: tachycardia, muscle tremor

First class are the β₂-agonists. β₂-Agonists work to cause bronchodilation by relaxing bronchial smooth muscle at the adrenergic receptor. β₂-Agonists are classified as either short-acting, and I’ve given some examples here, or long-acting. Short-acting β₂-agonists are the primary rescue therapy used by patients with either asthma or COPD; whereas long-acting β₂-agonists are used on a more chronic basis in those diseases.

The common side effects that this class of agents can cause include tachycardia, or an increase in heart rate, and a fine skeletal muscle tremor.
Changes in Albuterol Availability

- After December 2008, Chlorofluorocarbon (CFC) containing albuterol products are banned in the U.S.
- Spot shortages of albuterol MDI (CFC and non-CFC) are expected during the transition period.
- Hydrofluoroalkane (HFA)-containing albuterol MDIs are equally safe and effective as the CFC-containing products.
The next class of agents are the anticholinergics. Anticholinergic agents are delivered by inhalation therapy for patients with lung disease as well, and they result in bronchodilation by relaxing bronchial smooth muscle by inhibiting action at the cholinergic receptor.

Currently, we have two agents that are anticholinergics: the short-acting ipratropium bromide, or the long-acting tiotropium. These agents are used primarily in the treatment for COPD; although ipratropium is used for acute asthma, especially for patients in the emergency department or the hospital. Inhaled anticholinergics are very well tolerated with the most common side effect being a complaint of dry mouth.
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Long-acting Bronchodilators

• Long-acting Beta$_2$ agonists
  – Includes: arformeterol, formoterol, salmeterol
  – Side effects: tachycardia, black box warning (relevant for asthma)

• Long-acting Anticholinergic
  – Tiotropium
  – Side effects: dry mouth
Significant Issues in COPD Pharmacotherapy

• Which long-acting bronchodilator should be used first?
• Are combinations of long-acting bronchodilators beneficial and cost-effective?
• When should inhaled corticosteroids be introduced into the regimen?
Sin et al collected data from several trials and reviews conducted during the years from 1980 to 2002. Compilation of this data was used to evaluate various interventions used for individuals diagnosed with COPD. A meta-analysis was done on the data from 7 clinical trials which studied the effects of long-acting $\beta_2$-Antagonists (LABAs) on the relative risk of exacerbations for individuals with COPD. LABAs began to be used in an effort to improve lung function in a longer lasting and more predictable manner than what was currently being produced by using short-acting $\beta_2$-Antagonists. Data from Wadbo et al (N=183), van Noord et al (N=144), Chapman et al (N=408), Rossi (N=854), Dahl et al (N=780), Aalbers et al (N=687), Rennard et al (N=405), and Mahler et al (N=411) combined to show a 21% reduction in exacerbation rates associated with use of LABAs as compare to placebo for individuals with moderate to severe COPD, relative risk of exacerbation ranging from 0.13 to 1.88 (95% confidence interval, 10%-31%).

Sin et al performed a meta-analysis of data from 8 trials of patients with moderate to severe COPD that assessed how long-acting $\beta_2$-Agonists (LABA) affect exacerbations. The overall reduction in COPD exacerbation rates calculated with the data from Wadbo et al, vanNoord et al, Chapman et al, Rossi et al, Dahl et al, Aalbers et al, Rennard et al, and Mahler et al was 21% (95% CI, 10%-31%).
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Theophylline

- Primary action is bronchodilation due to various mechanisms including inhibiting adenosine
- Exerts modest anti-inflammatory actions
- Significant intrapatient and interpatient variability in dosage requirements and frequent risk for drug interactions
- Common side effects: gastrointestinal, cardiac, central nervous system

The next class of medication used for asthma and COPD are the methylxanthines or theophylline. Theophylline works as a bronchodilator by a variety of mechanisms including the inhibition of adenosine, another endogenous bronchoconstrictor. Theophylline's also been shown to exert some modest anti-inflammatory effect in the airway.

Theophylline is a difficult drug to use because there's significant intrapatient and interpatient variability in both dosage requirements and ultimate clearance from the body. Theophylline also has the potential risk for frequent drug interactions.

Common side effects associated with theophylline therapy that limits its use include side effects in the gastrointestinal tract, the cardiac system, and the central nervous system.
Theophylline in COPD
Current Role

• Often 3rd line
• Bronchodilator and anti-inflammatory actions
• Added to other therapies
• Deterioration occurs when withdrawn
• May benefit small airways (systemic administration)
• No role in acute exacerbation

And in summary, patients with COPD are treated with pharmacotherapy according to the stage of their disease. The initial treatment of COPD, from a pharmacologic perspective, typically focuses on bronchodilator therapy; although patients who suffer frequent exacerbations may benefit from the use of inhaled corticosteroids. Patients with the most severe form of COPD may require supplemental oxygen therapy, or in some cases, surgical options along with pharmacologic therapy.
Manage Stable COPD
Inhaled Corticosteroids

- Regular treatment with inhaled glucocorticosteroids is appropriate for symptomatic COPD patients with an FEV$_1$ < 50% predicted (*Stage III: Severe COPD* and *Stage IV: Very Severe COPD*) and repeated exacerbations *e.g.* 3 in the last three years.
- This treatment has been shown to reduce the frequency of exacerbations and improve health status.
The next major class of agents are the inhaled corticosteroids. Corticosteroids work against inflammation at the cellular level at the steroid receptor. There are several corticosteroid products available on the market in the United States, and these differ primarily by milligram potency.

Inhaled corticosteroids are the primary therapy for patients with asthma and they are also beneficial for some patients with COPD when used in combination with bronchodilators. To reduce the systemic effects of corticosteroids, these products are frequently used with spacer devices or a mouth rinsing procedure to reduce systemic side effects. The common local side effects associated with inhaled corticosteroids are complaints of a sore throat or hoarseness.
Inhaled Steroids (ICS) in Stable COPD

- Regular treatment with ICS does not modify the long-term decline in FEV\textsubscript{1}.
- Appropriate for symptomatic COPD patients with an FEV\textsubscript{1} < 50% and repeated exacerbations (Stage III and IV).
- ICS reduce frequency of exacerbations and improve health status.
- ICS combined with long-acting β\textsubscript{2}-agonist more effective than individual components.

ISOLDE trial pts with fev1 50% predicted had 25% less exacerbations
ICS and Acute Exacerbations of COPD:

Meta-Analysis

Relative Risk of Exacerbations in Patients With COPD Treated With Inhaled Corticosteroids vs Placebo

Vestbo et al
Bourbeau et al
Burge et al
Lung Health Study
Weir et al
Paggiaro et al
Overall

0.0 0.5 1.0 1.5 2.0 2.5 3.0
Relative Risk

ICS and Mortality in COPD

COPD Mortality Based on Time to Introduction of ICS Therapy following Hospitalization

Macie, C. et al. Chest 2006;130:640-646
Significant Issues in COPD Pharmacotherapy

- Which long-acting bronchodilator should be used first?
- Are combinations of long-acting bronchodilators beneficial and cost-effective?
- When should inhaled corticosteroids be introduced into the regimen?
Potential COPD Combination Therapies
(each with SABA as needed)

- Short-acting anticholinergic + SABA scheduled
- LABA + short-acting anticholinergic
- LABA
- Tiotropium
- LABA + tiotropium
- LABD + ICS
- LABD combination + ICS
- Any of the above + oral theophylline

LABD: Long-acting bronchodilator.

There are a variety of combination therapies that can be used for patients with varying degrees of COPD. A short-acting anticholinergic agent can be used with a short-acting $\beta_2$-agonist. A long-acting $\beta_2$-agonist can be used alone or in combination with a short-acting anticholinergic therapy. Another option would be the use of a long-acting anticholinergic therapy such as tiotropium.

In some cases, a long-acting $\beta_2$-agonist can be combined with the long-acting anticholinergic tiotropium. Or, long-acting bronchodilator therapies can be combined with inhaled corticosteroid therapy directed against the inflammatory components of COPD. Or, long-acting bronchodilator therapies could be used in combination along with anti-inflammatory therapies.

In patients who can’t be controlled with other means, any of the combinations of above could be used in combination with oral theophylline therapy.
Major Trials in COPD

- **TORCH** (Towards a Revolution in COPD Health) (recently completed)
  - Salmeterol and Fluticasone

- **UPLIFT** (Tiotropium and its Effect on Rate of Decline of FEV$_1$)(ongoing)
  - Tiotropium
TORCH COPD Study

- 6,100 subjects received salmeterol, fluticasone, combo, or placebo.
- Salmeterol/Fluticasone (50/500) showed a 17% relative reduction in mortality over 3 years in COPD compared with placebo.
Hospitalization due to COPD: Tiotropium vs. Placebo

* Log Rank Test

Casaburi ERJ 2002;19:217
COPD: Tiotropium + Formoterol

Other Management Considerations
Oxygen Therapy in Stable COPD

- The long-term administration of oxygen (>15 hours per day) to patients with chronic respiratory failure has been shown to increase survival.
- Improvement in quality of life in patients with severe COPD and chronic hypoxemia (partial pressure of arterial oxygen, <55 mm Hg).
Pulmonary Rehabilitation

- Pulmonary rehabilitation consisting of a structured program of education, exercise, and physiotherapy has been shown in controlled trials to improve exercise capacity and quality of life among patients with severe COPD and to reduce the amount of health care needed.
Lung Volume Reduction Surgery

- National Emphysema Treatment Trial Research Group
- 1,218 patients with severe emphysema underwent pulmonary rehabilitation and were randomly assigned to undergo lung-volume reduction surgery or to receive continued medical treatment
- Increases chance of improved exercise capacity but does not confer a survival advantage
- Survival advantage for patients with predominantly upper-lobe emphysema and low base-line exercise capacity
Manage Exacerbations
Key Points

- Exacerbations of respiratory symptoms requiring medical intervention are important clinical events in COPD.

- The most common causes of an exacerbation are infection of the tracheobronchial tree and air pollution, but the cause of about one-third of severe exacerbations cannot be identified.
COPD Exacerbation

- A sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD. It frequently requires the patient to seek medical attention or alter treatment.

Components of Treatment: Acute Exacerbations

- Intensify treatment with bronchodilators
- Consider using nebulizer if MDI cannot be used effectively
- Short course systemic corticosteroids
- Consider antibiotics if change in sputum volume, purulence, or increased dyspnea
- Supplemental oxygen therapy
- Treat co-morbidities or other contributory exacerbators of COPD

http://www.ogp.med.va.gov/cpg/copd/archive/module_b/b2.htm
Co-Morbid Conditions that can Impact COPD Exacerbation Management

- Congestive heart failure
- Pneumonia
- Pulmonary embolism
- Spontaneous pneumothorax
- Inappropriate oxygen therapy
- Psychotropic drugs (hypnotics, tranquilizers, narcotics, etc.)
- Drug allergy (penicillin, cephalosporin, etc.)
- Metabolic disease (diabetes mellitus, electrolyte disorders)
- Poor nutritional status
- Myopathy (e.g., steroid myopathy)
- Other acute illness (acute abdomen, GI hemorrhage, CVA, etc.)

http://www.oqp.med.va.gov/cpg/copd/archive/module_b/b2.htm
Manage Exacerbations

Key Points

- Non-invasive intermittent positive pressure ventilation (NIPPV) in exacerbations improves blood gases and pH, reduces in-hospital mortality, decreases the need for invasive mechanical ventilation and intubation, and decreases the length of hospital stay.
Components of COPD Management

- Patient education
- Assess and monitor disease
- Reduce risk factors
- Manage stable COPD
- Manage exacerbations
New Anti-inflammatory Drugs In Development

- Phosphodiesterase 4 inhibitors, which have an inhibitory effect on key inflammatory cells involved in COPD, including: macrophages, neutrophils, and cytotoxic T lymphocytes. (Cilomilast, Roflumilast)
  - A limitation of drugs in this class is the common side effect of nausea.
- Other novel anti-inflammatory approaches under development include: inhibitors of NF-(kappa)B, inhibitors of p38 mitogen-activated protein kinase, and interleukin-10
Medication Therapy Management Activities

- Educating the patient
  - Understanding of therapy
  - Arranging for drug therapy monitoring
  - Reinforcing proper use of all medications and related equipment
  - Achieving patient understanding

- Ensuring medications, equipment, supplies received by patient in timely fashion

- Documenting steps to implement plan
  - Baseline monitoring
  - Barriers

- Reducing risks and exposures

- Communicating plan to patient and other clinicians
Medication Management and Related Services for the COPD Patient

- Tobacco cessation counseling and risk factor avoidance
- Immunizations
- Recommendation and selection of medication and device products
- Education about proper use of medication
- Monitoring for safety and efficacy of therapy
- Considering therapeutic alternatives and cost
Medication Management and Related Services for the COPD Patient (continued)

- Monitoring co-morbidities and potential interactions
- Provision and monitoring of oxygen therapy
- Provision of home care equipment and supplies
- Referral to other community services and resources
Key educational messages for COPD

- **Stage 0**
  - Information/advice about risk reduction

- **Stage 1-3**
  - Information about disease
  - Inhaler skills/adherence
  - Recognize exacerbations
  - Minimize dyspnea

- **Stage 4**
  - Complications
  - Oxygen therapy
  - Advance directives/end of life decisions
COPD: The Current View

- Emerging evidence about the value of various pharmacotherapies
- Renewed optimism for the patient
- Numerous opportunities for the pharmacist to assist the patient in achieving optimal outcomes