Understanding COPD Pathophysiology and the Rationale for Use of Different Therapeutic Agents

September 10, 2013 • 2:00 PM–3:00 PM EDT

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Development and Support

Developed by the American Pharmacists Association

Supported by an independent educational grant from Boehringer Ingelheim Pharmaceuticals, Inc.

CPE Information

- Target Audience: Pharmacists
- ACPE#: 0202-0000-13-198-L01-P
- Activity Type: Knowledge-based

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Dennis Williams, PharmD, declares that his spouse/partner is an employee and stock/shareholder of GlaxoSmithKline.

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Objectives

At the end of this session, the participant will be able to:

- Explain chronic obstructive pulmonary disease (COPD) pathophysiology, including the cholinergic, sympathomimetic, and inflammatory components
- Identify medications used to treat COPD and describe the rationale for the use of therapeutic agents with different mechanisms of action
- Explain how the pharmacist can work with prescribers to ensure optimal COPD therapy

Question 1

The increase in vagal tone that is observed in patients with COPD results in:

a. Increased airway diameter
b. Decreased airway diameter
c. Increased mucus production
d. Decreased mucus production
Question 2
The effectiveness of tiotropium as a bronchodilator is based on the:

a. Selective binding and inhibition at the $M_3$ receptor in the airway
b. Binding and inhibition of all muscarinic receptors in the airways
c. Selective binding and activation of the $M_2$ receptor in the airway
d. Activation of adrenergic receptors in the airways

Question 3
The most important determinant of the effectiveness of medications for COPD delivered via inhalation is the:

a. Bioavailability from the lung
b. pH of the inhaled molecule
c. Technique of inhalation
d. Patient age

Chronic Obstructive Pulmonary Disease

“Chronic Obstructive Pulmonary Disease (COPD), a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients.”
Prevalence of Chronic Obstructive Pulmonary Diseases

- Chronic respiratory diseases (primarily COPD) are the 3rd leading cause of death in the United States
- Affects 15 million Americans (6.3% of population), with women (6.7%) reporting higher prevalence than men (5.2%)
- Prevalence is 11.6% for ages 65 years and older
- Prevalence in smokers is higher (13.3%) compared with former smokers (6.8%) or never smokers (2.8%)


COPD

- A reported 20% of patients with a COPD diagnosis have not undergone spirometry
- Another 24 million people have evidence of impaired lung function but not a COPD diagnosis


Causes of COPD

Etiologies

- Cigarette smoking represents 88% of cases
- All other causes represent 12%
* Includes: Other Environmental and Occupational Inhalation Exposures

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Inflammation in COPD

- Activates Respiratory Tract Macrophages
- Release Proteases
- Resulting in Airway and Parenchymal Damage

Protease-Antiprotease Imbalance in COPD

- Proteases:
  - Neutrophil elastase
  - Cathepsins
  - Matrix metalloproteinases
- Antiproteases:
  - α1-Antitrypsin
  - Elafin
  - Secretory leukoprotease inhibitor
  - Tissue inhibitors of matrix metalloproteinases

Consequences of Chronic Inflammation in COPD

- Small Airway Disease:
  - Inflammatory response
  - Airway remodeling
- Parenchymal Destruction:
  - Loss of alveolar attachments
  - Decreased elastic recoil
- Chronic Airflow Limitation
Summary of COPD Pathophysiology

- Airflow limitation (obstruction) in COPD is chronic and progressive based on continued exposure to the inciting factor
- Airflow limitation is related to reduced airway diameter, inflammation, increased mucus production, structural destruction, and fibrosis
- Hyperresponsiveness of the airways is not a factor for many patients with COPD

Diagnosis of COPD

- COPD should be considered in any patient with:
  - History of exposure to risk factors (especially cigarette smoke)
  - Cough (sputum)
  - Dyspnea
  - Cough and sputum production may precede development of airflow limitation
  - Obtain spirometry testing

Spirometry in COPD Diagnosis

- Spirometry is essential as the gold standard for diagnosis
- Spirometry is standardized, reproducible, and objective
- Peak flow meter use has limited value
- Other components in the medical history also are important for diagnosis
- Spirometry greatly underutilized
**Spirometry Testing is Important for the Diagnosis, Grading, and Monitoring of COPD**


**Possible Progression of COPD in Smokers**

- Evidence of physiological damage

**COPD: Severity of Chronic Disease**

- Three components determine severity
  - Spirometry to assess degree of airflow limitation
  - Symptoms assessment (various tools)
  - Risk for exacerbations

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COPD Classification Criteria

- **C**
  - High risk
  - Less symptoms
  - MMRC < 2
  - CAT < 10
  - Spruymetric Grade 1
  - Exacerbations per Year 0

- **D**
  - High risk
  - More symptoms
  - MMRC ≥ 2
  - CAT ≥ 10
  - Spruymetric Grade 2
  - Exacerbations per Year 1 - 2

- **A**
  - Low risk
  - Less symptoms
  - MMRC < 2
  - CAT < 10
  - Spruymetric Grade 0
  - Exacerbations per Year 0

- **B**
  - Low risk
  - More symptoms
  - MMRC ≥ 2
  - CAT ≥ 10
  - Spruymetric Grade 1
  - Exacerbations per Year 1

MMRC = Modified Medical Research Council Dyspnea Scale
CAT = COPD Assessment Test
GOLD Guidelines 2013. [Link](http://www.goldcopd.org/Guidelines/guidelines-resources.html)

Treatment Goals for Stable COPD

**Reduce Symptoms**
- Relieve symptoms
- Improve exercise tolerance
- Improve overall health status

**Reduce Risks**
- Prevent disease progression
- Prevent and treat exacerbations
- Reduce mortality
- Prevent and treat complications
- Minimize adverse effects

2013 GOLD COPD Guidelines available at: www.goldcopd.org

Pharmacotherapy Recommendations for COPD

<table>
<thead>
<tr>
<th>Patient Group (Classification)</th>
<th>Recommended 1st Choices</th>
<th>Alternative Choices</th>
<th>Other Options</th>
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<tbody>
<tr>
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<td>Short-acting anticholinergic, LABA, or ICS-LABA</td>
<td>Long-acting anticholinergic, LABA</td>
<td>Transfusione</td>
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Pharmacotherapy for COPD

- Primary medications for chronic COPD treatment work as:
  - Bronchodilators
    - By relaxing bronchial smooth muscle that surrounds the airways
  - Anti-inflammatories
    - By suppressing inflammatory cells and mediators

Autonomic Physiology of the Airways

- Cholinergic innervation of bronchial smooth muscle is a major determinant of bronchomotor tone
  - Muscarinic (M3) receptors are present on bronchial smooth muscle in large and, to a lesser extent, small airways
  - There is minimal direct adrenergic innervation of bronchial smooth muscle
    - Beta2 (β2) adrenergic receptors are present on bronchial smooth muscle in large and small airways as well as on selected target cells (e.g., mast cells)


Bronchomotor Tone Is Increased in COPD

Rutlege RD. Use of Inhaled Anticholinergic Agents in Obstructive Airway Disease. Respir Care 2007;52(7):653-651.
Bronchodilators for COPD

- Bronchodilators are the primary therapies used in the management of COPD
- Act by relaxing bronchial smooth muscle and increasing the diameter of the airway lumen
- Effect can be achieved by activating $\beta_2$-adrenergic receptors or inhibiting M3 receptors on bronchial smooth muscle

$\beta_2$-Adrenergic Agonists

**Mechanism of Action**

- **Adenyl Cyclase**: Increases bronchial smooth muscle relaxation and bronchodilation


$\beta_2$-Adrenergic Agonists

- **Short-acting agents**
  - Albuterol
  - Levalbuterol
  - Pirbuterol
- **Long-acting agents** (based on longer residence time at the $\beta_2$-adrenergic receptor)
  - Arformoterol
  - Formoterol
  - Indacaterol
  - Salmeterol
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Anticholinergics
Mechanism of Action

- **M2 Receptor** (Inhibitory)
- **M3 Receptor** (Stimulatory)

Bronchial Smooth Muscle

Acetylcholine

Results in Bronchoconstriction

Blocked by Anticholinergics

Vagal Nerve Terminal


Anticholinergic Agents

- **Short-acting agent**
  - Ipratropium

- **Long-acting agents (based on longer residence time at muscarinic receptor and improved selectivity for M3 receptor)**
  - Aclidinium
  - Tiotropium

Anticholinergic Agents

- Side effects are also related to muscarinic-blocking actions
  - Dry mouth
  - Blurred vision (not common but possible)
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Mechanism for Bronchodilators
Relieving Dyspnea in COPD

Long-Acting Bronchodilators:
β₂-Agonists and Anticholinergics

- For patients with chronic symptoms and/or frequent use of short-acting bronchodilators, these agents:
  - Are more effective at relieving symptoms and improving lung function
  - Are more convenient to use
  - Reduce exacerbation frequency

Choosing a Long-Acting Bronchodilator

- Expert guidelines do not favor one class over the other
- Long-acting β₂-agonists
  - Salmeterol, formoterol, arformoterol, indacaterol
- Long-acting anticholinergic agents
  - Tiotropium, aclidinium
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Corticosteroids
Mechanism of Action

Corticosteroid Agents
- Beclomethasone
- Budesonide
- Ciclesonide
- Fluticasone (various salts)
- Mometasone

Corticosteroid Agents
- Inhaled agents indicated for chronic use in COPD
- Best evidence for Grades 3 and 4 as well as for patients with frequent exacerbations
- Increased risk of respiratory infections in patients with COPD
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Phosphodiesterase-4 Inhibitors

- Roflumilast
  - Oral therapy indicated for patients with chronic bronchitis who experience frequent exacerbations
  - Most common side effect is nausea/vomiting
  - May be associated with excessive weight loss or personality changes

Combination Inhalers for COPD

- Albuterol and ipratropium
- Budesonide and formoterol
- Fluticasone propionate and salmeterol
- Fluticasone furoate and vilanterol
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### COPD Classification Criteria

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**C** High risk, Less symptoms

**D** High risk, More symptoms

**A** Low risk, Less symptoms

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**MMRC** = Modified Medical Research Council Dyspnea Scale

**CAT** = COPD Assessment Test


### Pharmacotherapy Recommendations for COPD

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- Short-acting β₂-agonist PRN | Long-acting anticholinergic  
Long-acting β₂-agonist  
Long-acting anticholinergic and short-acting anticholinergic in tandem | Theophylline |
| B                             | - Long-acting anticholinergic  
- Long-acting β₂-agonist | Long-acting anticholinergic  
Long-acting β₂-agonist plus Long-acting β₂-agonist  
Either of the above agents with phosphodiesterase-4 inhibitor | Short-acting anticholinergic, Short-acting β₂-agonist  
Short-acting anticholinergic plus Long-acting β₂-agonist  
Theophylline |
| C                             | - Inhaled corticosteroid plus Long-acting β₂-agonist  
- Long-acting anticholinergic | Long-acting anticholinergic and phosphodiesterase-4 inhibitor  
Either of the above agents with phosphodiesterase-4 inhibitor | Short-acting anticholinergic  
Long-acting anticholinergic and Long-acting β₂-agonist  
Theophylline |
| D                             | - Inhaled corticosteroid plus Long-acting β₂-agonist  
- Long-acting anticholinergic and phosphodiesterase-4 inhibitor  
Control of both above  
Combination therapy | Either of the above agents with phosphodiesterase-4 inhibitor  
Short-acting anticholinergic and Long-acting β₂-agonist  
Theophylline |


### Pharmacists’ Role in Optimizing Outcomes for Patients With COPD

- Identify patients with risk factors
- Encourage (and consider performing) spirometry testing
- Assist patients with smoking cessation
- Provided vaccines to protect against influenza and pneumococcal disease
- Collaborate with other clinicians to determine optimal pharmacotherapy regimens
- Explain the rationale for various medications
Assisting Patients With COPD Medication Use

- Educate patient regarding the role and proper use of each therapy
- Assess safety and effectiveness of medication regimen
- Monitor for drug interactions
- Periodically assess patient understanding, adherence, and ability to use inhalation therapies
- Provide care and services for all stages of COPD

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