Breathing Easy: Updates in Current Management of COPD

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Pharmacist Objectives

• Assess new GOLD recommendations for COPD management
• Evaluate new treatment options and inhaler devices for COPD
• Formulate factors that help aid in the selection of specific treatment options for COPD

Pharmacy Technician Objectives

• Identify different inhaler devices for patients with COPD
• List appropriate counseling points for specific inhalers
• Identify patient factors that may help aid in the selection of specific treatment options

COPD Definition

- Common, preventable, treatable disease
- Characterized by persistent respiratory symptoms and airflow limitation
- Symptoms due to airway and/or alveolar abnormalities

Epidemiology

- >15 million Americans
  - Under-recognized and under-diagnosed
- Major cause of morbidity
  - Increases with age
- Significant mortality
  - Now the 3rd leading cause of death in the US

COPD Rates in Michigan

COPD Prevalence in Adults by State, 2013

[Map showing COPD prevalence by state in Michigan, with 2013 data]
## Etiology

### Cigarette smoking
- Responsible for 85-90% of cases

### Exposures
- Environmental tobacco smoke
- Occupational dusts and chemicals
- Air pollution

### Host factors
- Genetic predisposition (alpha-1 antitrypsin deficiency)
- Airway hyperresponsiveness
- Impaired lung growth
- Age

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## Pathophysiology

### Etiology
- Exposure to noxious particles

### Host factors

### Pathophysiology
- Impaired lung growth
- Lung and systemic inflammation
- Accelerated decline

### Emphysema
- Parenchymal tissue destruction

### Small airway fibrosis
- Disruption of normal repair and defense mechanisms

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## Clinical Presentation

### Dyspnea
- Persistent
- Characteristically worse with exercise
- Progressive and worse over time

### Chronic cough
- May be intermittent and unproductive

### Chronic sputum production
- Any pattern of chronic sputum production

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## Diagnosis

### Spirometry
- FVC: amount of air exhaled as long as forcefully as possible
- FEV₁: amount of air exhaled during the first second of the FVC maneuver
- FEV₁/FVC: ratio used to determine if pattern is obstructive, restrictive, or normal

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## 2017 Guideline Updates
Changes in 2017 Guidelines

- Staging/classification based on ABCD assessment tool
- Shift toward more individualized treatment with integrated care
- Symptoms and exacerbation risk guide treatment
- Emphasis on inhaler technique

ABCD Assessment Tool

1. Confirm diagnosis by spirometry
2. Assess airflow limitation
3. Assess symptoms & risk of exacerbations

<table>
<thead>
<tr>
<th>GOLD Grade</th>
<th>FEV1 (% predicted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOLD 1</td>
<td>≥ 80</td>
</tr>
<tr>
<td>GOLD 2</td>
<td>50-79</td>
</tr>
<tr>
<td>GOLD 3</td>
<td>30-49</td>
</tr>
<tr>
<td>GOLD 4</td>
<td>&lt; 30</td>
</tr>
</tbody>
</table>

Exacerbation History

- 2 or 3 in 1 leading to admission
- 1 (not leading to admission)

Symptoms & exacerbation risk

- GOLD 1
- GOLD 2
- GOLD 3
- GOLD 4

Modified British Medical Research Council (mMRC) Questionnaire

<table>
<thead>
<tr>
<th>mMRC Grade</th>
<th>Level of breathlessness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td>I only get breathless with strenuous exercise</td>
</tr>
<tr>
<td>Grade 1</td>
<td>I get short of breath when hurrying on the level or walking up a slight hill</td>
</tr>
<tr>
<td>Grade 2</td>
<td>I walk slower than people of the same age on the level because of breathlessness, or have to stop for breath when walking on my own pace on the level</td>
</tr>
<tr>
<td>Grade 3</td>
<td>I stop for breath after walking about 100 meters or after a few minutes on the level</td>
</tr>
<tr>
<td>Grade 4</td>
<td>I am too breathless to leave the house or I am breathless when dressing or undressing</td>
</tr>
</tbody>
</table>

COPD Assessment Test (CAT)

- Comprehensive test
- Score ranges 0-40
- Applicable worldwide
- Available in several validated translations

St. George's Respiratory Questionnaire (SGRQ)

- 50-item questionnaire
- Three component scores are calculated
  - Symptoms
  - Activity
  - Impacts
- One total score is also calculated

Audience Participation

Which of the following factors must be considered when assessing and staging a patient’s severity of COPD?

a. Spirometry
b. Airflow limitation
c. Symptoms
d. Risk of exacerbations
e. All of the above
Changes in 2017 Guidelines

- Staging/classification based on ABCD assessment tool
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- Symptoms and exacerbation risk guide treatment
- Emphasis on inhaler technique

Treatment Goals: Stable COPD

- REDUCE SYMPTOMS
  - Relieve symptoms (SOB, sputum production, etc.)
  - Improve exercise tolerance
  - Improve health status

- REDUCE RISK
  - Prevent disease progression
  - Prevent and treat exacerbations
  - Reduce mortality

Non-Pharmacologic Treatment

- Smoking Cessation
  - Counseling
  - Nicotine replacement therapy

- Preventive Care
  - Minimize second hand smoke and occupational fumes
  - Monitor pollution index and stay indoors when pollution is high

- Vaccinations
  - Influenza
  - Pneumococcal

- Supportive Care
  - Regular physical activity
  - Oxygen
  - Pulmonary rehabilitation

Pharmacologic Options for Stable COPD

- Bronchodilators
  - Short-acting beta agonists (SABA)
  - Long-acting beta agonists (LABA)
  - Short-acting antimuscarinic (SAMA)
  - Long-acting antimuscarinic (LAMA)
  - Methylxanthines

- Anti-Inflammatory Therapy
  - Inhaled Corticosteroids (ICS)
  - Oral glucocorticoids
  - Phosphodiesterase-4 inhibitors
  - Antibiotics
  - Mucolytics

Pharmacologic Treatment: Inhalers

Pharmacology

- LABAs
  - Target B2 receptors throughout the lungs and distal airways

- LAMAs
  - Target M3 receptors, more concentrated in proximal airways

Dual Bronchodilation
Dual Benefit

LABAs

LAMAs

2017 Treatment Algorithm

Group C

Group D

Group A

Group B

A bronchodilator

Evaluate effect

Further exacerbation(s)

A long-acting bronchodilator (LABA or LAMA)

Persistent symptoms

Evaluate effect

Further exacerbation(s)

Persistent symptoms

LABA + LAMA

Consider ICS

Consider ICS

Consider ICS

Consider ICS

LABA + ICS

LABA + ICS

LABA + ICS

LABA + ICS

Global Strategy for the Diagnosis, Management and Prevention of COPD. Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017

* if FEV1 < 50% predicted and patient has chronic bronchitis

^ former smoker

Audience Participation

According to the 2017 GOLD Guidelines, which of the following is the appropriate treatment strategy for a patient in Group B who is currently on a LABA inhaler, but now experiencing increased symptoms?

a. Discontinue the LABA and start a LAMA
b. Add an ICS
c. Add a LAMA
d. Add a LAMA and an ICS

LABA/LAMA Combination Inhalers

LABA/LAMA Combination Inhalers

General Considerations

Interactions

• Concomitant anticholinergic use
• MAOIs and TCAs
• Beta-blockers
• Non-potassium sparing diuretics

Precautions

• Worsening of narrow-angle glaucoma and urinary retention
• Hypokalemia and hyperglycemia

Warnings

• Do not initiate in acutely deteriorating patients
• Not for relief of acute symptoms
• LABAs contraindicated in patients with asthma without use of long-term controller

Vilanterol/Umeclidinium (Anoro Ellipta)
Ellipta® Device
• Requires no hand-breath coordination
• Single-step dose activation
• Opening and closing cover will result in lost dose if not inhaled
• Patients report improved ease-of-use compared to diskus

Vilanterol/Umeclidinium (Anoro Ellipta)

Dosing
• 1 inhalation (25 mcg/62.5 mcg) once daily (DPI formulation)

Pharmacokinetics
• Metabolism: CYP3A4 (VI); CYP2D6 (UMEC)

Adverse Effects
• Pharyngitis, sinusitis, lower respiratory tract infections, constipation/diarrhea, pain in extremities, muscle spasms, neck and chest pain

Contraindications
• Contraindicated if severe hypersensitivity to milk proteins or ingredients/excipients

Drug Interactions
• Strong CYP3A4 inhibitors: use with caution

Vilanterol/Umeclidinium (Anoro Ellipta)
Donohue et al.
Study Design
24-week randomized, double-blind, placebo-controlled, parallel group study

Patients
N = 1532 patients with moderate to very severe COPD

Interventions
• Treatment groups
  • UMEC/VI 62.5 mcg/25 mcg
  • UMEC 62.5 mcg
  • VI 25 mcg
  • Placebo

Outcomes
• Improved FEV1 in all groups compared to placebo
• No safety differences
• HRQoL similar in all active treatment groups
• Decreased exacerbations?

Vilanterol/Umeclidinium (Anoro Ellipta)
Decramer et al.
Study Design
24-week replicate study that included an active control

Patients
Patients with moderate to very severe COPD
N = 846 in study 1; N = 872 in study 2

Interventions
Study 1: UMEC/VI (2 doses), TIO, VI monotherapy
Study 2: UMEC/VI (2 doses), TIO, UMEC monotherapy

Outcomes
Study 1: UMEC/VI (2 doses) had greater improvement in FEV1 compared to TIO and VI (p <0.005)
Study 2: UMEC/VI (2 doses) had greater improvement in FEV1 compared to TIO (p < 0.05), but not UMEC (p = 0.38)
No difference between active treatments in dyspnea, HRQoL, or exacerbations

Olopatadine/Tiotropium (Stiolto Respimat)

• Reduces oropharyngeal medication deposition
• Approximately 75% of particles are absorbed
• Proven efficacy with lower doses of medication
• May not be easily used by all patients

Olodaterol/Tiotropium (Stiolto Respimat)

**Dosing**
- 2 inhalations (each 2.5 mcg/2.5 mcg) once daily (Respimat formulation)

**Pharmacokinetics**
- Metabolism: glucoronidation, o-demethylation (Olo); partly hepatic (25%) but excreted mostly unchanged (Tio)

**Adverse Effects**
- Nasopharyngitis, cough, and back pain

**Contraindications/Precautions**
- Contraindicated if hypersensitivity to any ingredients or excipients; immediate hypersensitivity reactions occurred in clinical trials
- Patients with renal impairment should be monitored for anticholinergic side effects


Indacaterol/Glycopyrrolate (Utibron Neohaler)

**Dosing**
- Inhalation contents of 1 capsule (27.5 mcg/15.6 mcg) twice daily (neohaler formulation)

**Pharmacokinetics**
- Metabolism: UGT1A1 and CYP3A4 (Indacaterol); minimal (Glyco)

**Adverse Effects**
- Nasopharyngitis, hypertension

**Contraindications/Precautions**
- Contraindicated if hypersensitivity to any ingredients or excipients; immediate hypersensitivity reactions occurred in clinical trials
- Use in patients with severe renal impairment should be considered only if benefit outweighs risk


FLIGHT 1 & 2

**Study Design**
- Two 12-week replicate randomized, double-blind, parallel group, placebo and active-controlled studies

**Patients**
- N = 2038 patients with moderate to very severe COPD

**Interventions**
- Treatment groups (all given BID via neohaler)
  - Indacaterol/Glycopyrrolate 27.5/15.6 mcg
  - Indacaterol 27.5 mcg
  - Glycopyrrolate 15.6 mcg
  - Placebo

**Outcomes**
- Improved FEV₁, in all groups with combination
- No safety differences
- HRQoL improved vs. mono-components

Formoterol/Glycopyrrolate (Bevespi Aerosphere)

Co-Suspension™ Delivery Technology

Dosing
- 2 inhalations (4.8 mcg/9 mcg each) twice daily; pMDI (pressurized MDI)
- Unique Co-Suspension™ Delivery Technology

Pharmacokinetics
- Metabolism: direct glucuronidation and O-demethylation (Formoterol); minimal (Glyco)

Adverse Effects
- Urinary tract infection, cough, nasopharyngitis, sinusitis

Contraindications, Precautions
- Contraindicated if hypersensitivity to any ingredients or excipients

Martinez FJ, et al. CHEST 2017

Formoterol/Glycopyrrolate (Bevespi Aerosphere) [package insert]. AstraZeneca Pharmaceuticals LP, Wilmington, DE. 2016 May.

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Martinez FJ, et al. CHEST 2017

Formoterol/Glycopyrrolate (Bevespi Aerosphere)

Audience Participation

Which of the following factors are unique about Bevespi?

a. Inhaler device
b. Co-suspension technology
c. Dosing
d. Cost
## LABA/LAMA Combination Inhalers

<table>
<thead>
<tr>
<th>Device/Delivery</th>
<th>Anoro Ellipta</th>
<th>Stiolto Respimat</th>
<th>Ulturn Neohaler</th>
<th>Bevespi Aerosphere</th>
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<tr>
<td>Improved drug delivery with capsule</td>
<td>Improved drug delivery with Respimat</td>
<td>Improved drug delivery via new technology</td>
<td>More complex device use with capsule</td>
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<table>
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<th>1 inhalation twice daily</th>
<th>2 inhalations twice daily</th>
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<table>
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<table>
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<tr>
<th>HRQoL/symptoms</th>
<th>Similar</th>
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<table>
<thead>
<tr>
<th>Exacerbations</th>
<th>Decreased?</th>
<th>Decreased?</th>
<th>?</th>
<th>?</th>
</tr>
</thead>
</table>

## Benefits of LABA/LAMA Therapies

- Improved adherence
- Decreased complexity and cost
- Lower risk of adverse effects
- Improvement in symptoms

## Future Directions

- Approval of formoterol/aclidinium
- Further head to head studies
- Post-marketing experience

## LATE BREAKING: LABA/LAMA/ICS Combination Inhalers

Fluticasone/Vilanterol/Umeclidinium (Trelegy Ellipta)

- **Dosing**: 1 inhalation (100mcg/62.5 mcg/25mcg) once daily (DPI formulation)

- **Pharmacokinetics**: CYP3A4 (F and VI); CYP2D6 (UMEC)

- **Adverse Effects**:
  - Headache, back pain, dizziness, diarrhea, cough, oropharyngeal pain, and gastrointestinal

- **Contraindications**:
  - Contraindicated if severe hypersensitivity to milk proteins or ingredients/excipients

- **Drug Interactions**:
  - Strong CYP3A4 inhibitors: use with caution
  - MAOIs and TCAs: use with extreme caution

## Fluticasone/Vilanterol/Umeclidinium (Trelegy Ellipta)

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- **Drug Interactions**:
  - Strong CYP3A4 inhibitors: use with caution
  - MAOIs and TCAs: use with extreme caution
Fluticasone/Vilanterol/Umeclidinium (Trelegy Ellipta)

**Study Design**
- 24-week randomized, double-blind, double-dummy study

**Patients**
- N = 1,812 patients with COPD (GOLD group D)
  - CAT score ≥ 10 or ≥ 2 moderate exacerbations/1 severe exacerbation in the past year

**Interventions**
- Treatment groups received 24 weeks of:
  - Once daily FF/Umec/VI using Ellipta
  - Twice daily BUD/FOR and once-daily placebo using Ellipta
- Subset of patients remained on blinded treatment for up to 52 weeks

**Outcomes**
- Improved FEV1 at all time points during 24-week period
- Clinically significant improvements in SGRQ
- Decrease in incidence rates of moderate/severe exacerbations
- No safety differences

Changes in 2017 Guidelines

**Staging/classification based on ABCD assessment tool**
- Shift toward more individualized treatment with integrated care

**Symptoms and exacerbation risk guide treatment**
- Emphasis on inhaler technique

Therapy Considerations: Putting Guidelines into Practice

**Treatment Goals: Stable COPD**

REDUCE SYMPTOMS
- Relieve symptoms (SOB, sputum production, etc.)
- Improve exercise tolerance
- Improve health status

REDUCE RISK
- Prevent disease progression
- Prevent and treat exacerbations
- Reduce mortality

Pharmacotherapy for Stable COPD

- Disease State Control (symptoms/exacerbations)
- Cost
- Device (ability and preference)

Pharmacotherapy Factors to Consider

- Disease State Control (symptoms/exacerbations)
- Cost
- Device (ability and preference)

Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017

Meet AB

• AB is a 58 year old female who presents with complaints of increasing shortness of breath. Patient had a 22 year smoking history (1 pack per day). Quit smoking 5 years ago.
• Patient complains of increased shortness of breath; also notes that she has increased sputum production.
• Spirometry confirms a diagnosis of COPD
  - FEV1/FVC < 0.7
  - FEV1: 52%
  - CAT Score: 14
  - Patient has private insurance

How would you assess AB’s COPD? (GOLD grade and group)

Treatment for AB

• Which of the following medication classes are appropriate for AB?
  • LABA
  • LAMA
  • ICS
  • SABA
Types of Devices:
- Metered-dose Inhaler (MDI)
- Dry-powder Inhaler (DPI)
- Soft Mist Inhaler (SMI)
- Nebulized Solutions

Technique: the Basics

MDI
- Remove Cap
- Hold upright and shake well
- Breathe out gently
- Seal lips around mouth piece
- Start to slowly inhale and then press firmly down on canister
- Continue to breathe in slowly and steadily
- Hold breath for 10 seconds
- Wait 1 min between doses

DPI
- Load dose (differs for each device)
- Breath out gently, away from device
- Seal lips around mouth piece
- Breathe in steadily and deeply (more forcefully than the MDI)
- Hold breath for 10 seconds
- Breath out away from device

SMI
- Twist bottom of inhaler to prepare dose
- Open cap
- Breath out gently
- Seal lips around mouth piece
- Start to slowly inhale and press firmly down on the bottom
- Continue to breath in slowly and steadily
- Hold breath for 10 seconds
- Wait 1 min between doses

Technique: Points to Consider

MDI
- Breath/actuation coordination
- Force of breath and inhalation time
- Small dose counter

DPI
- Breath force to aerosolize powder
- Inhalation time important
- Some devices require opening a blister pack to prepare dose

SMI
- Multiple pieces that must be put together
- Requires some force to twist

Back to AB

- The provider asks you to recommend a device type for Ms. AB
- You determine that Ms. AB has mild arthritis in her hands that is worse in the winter months
- You also observe her inhalation forces and determine that she has appropriate inhalation force for all devices

Which inhaler device would you recommend for AB?

Inhalers: Factors to Consider

Disease State Control (symptoms/exacerbations)
- Cost
- Device (ability and preference)

Inhaler Cost Considerations

- Pulmonary patients pay ~$6000 more in medical costs annually
- Majority of inhalers are not generically available
  - Cash Price: $200-$400 per inhaler
- Insurance often put inhalers on Tier 3-4
  - Average out-of-pocket cost: $30-60 per inhaler
- Medicare patients typically pay higher copays and pay 45% of cash price once in the 'coverage gap'
- Studies demonstrate that when costs are controlled, COPD patients do better
**Cost-Avoidance Behaviors**

- Request generic formulations
- Use mail order pharmacies (or shop around for prices)
  - Transfer prescriptions frequently
  - Obtain medications from ‘across the border’
- Late for refills
  - Split doses/Skip doses
  - Completely stop medications
- Avoid new prescriptions (or prescriptions with higher copay)
  - Partial fills
  - Request coupons
- Other behaviors: share with their neighbors, buy on the street

**Identifying Cost Issues**

- Watch for cost-avoidance behaviors
- Target specific medications
- Flag prescriptions based on price during dispensing process
- “Develop the habit of routinely asking EVERY patient about the cost of his/her medication, if you don’t ask, you often will not be told”

**Key Takeaways**

- New staging/classification tool for COPD
- LABA/LAMA therapy earlier in disease state control
- Newer combination inhalers improve symptoms and FEV1
- Pharmacists can be a resource for inhaler teaching and cost reduction

**Breathing Easy:**

Updates in Current Management of COPD

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