Chronic Obstructive Pulmonary Disease: New Approaches to an Old Problem

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Chapel Hill, North Carolina
Target Audience: Pharmacists

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Activity Type: Application-based
Disclosure

• Dennis M. Williams: Glaxo Smith Kline (Spouse/Partner: 2 financial relationships declared - Employee, Stockholder/Ownership Interest [excluding diversified mutual funds])

• All other planners, presenters, and reviewers of this session report no financial relationships relevant to this activity.
Objectives

• Interpret data from clinical trials of newly-approved therapeutic approaches for Chronic Obstructive Pulmonary Disease (COPD).
• Describe recommendations in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease (COPD).
• Discuss the pros and cons of new and old approaches to managing COPD.
• Recommend appropriate therapy for COPD in patients across inpatient and outpatient settings.
GOLD Guidelines Update 2017
COPD Death Rates in the United States

Revisions to the GOLD Guidelines Pharmacotherapy

- Updated the definition of COPD
- Separated GOLD category from COPD severity group
- Added long-acting muscarinic antagonist (LAMA) and long-acting beta2 agonist (LABA) to mild COPD patients
- Removed inhaled corticosteroids (ICS) as preferred agents in group C and D
- Added azithromycin and erythromycin as alternative agents
- Emphasized inhaler technique teaching

Definition of COPD

• **Preventable**
• Noxious gases or particles
• Persistent respiratory symptoms
• Airflow limitation
• Airway and/or **alveolar abnormalities**
• Treatable

• **Pulmonary function testing**
  – DLCO- diffusing capacity of the lung for carbon monoxide
  – Identifies patients that may have alveolar abnormalities

Question 1: Which of the following GOLD grades and severity groups are appropriate for a 65-year-old with a COPD Assessment Test (CAT) score of 28 today, no COPD exacerbations in the past year and a forced expiratory volume in 1 second (FEV1) of 29% of the predicted value 1 month ago?

A. GOLD grade 4, group B
B. GOLD grade 4, group D
C. GOLD grade 1, group A
D. GOLD grade 1, group C

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### Severity of Airflow Limitation

**FEV1/Forced Vital Capacity (FVC) < 70%**

<table>
<thead>
<tr>
<th>GOLD Grade</th>
<th>Post-Bronchodilator FEV1 (% Predicted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Mild</td>
<td>≥ 80%</td>
</tr>
<tr>
<td>2 Moderate</td>
<td>50-79</td>
</tr>
<tr>
<td>3 Severe</td>
<td>30-49%</td>
</tr>
<tr>
<td>4 Very Severe</td>
<td>&lt; 30</td>
</tr>
</tbody>
</table>

# 2016 GOLD Guidelines Severity

<table>
<thead>
<tr>
<th>GOLD Grade</th>
<th>COPD Severity Group</th>
<th>Exacerbations within the past 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>C</td>
<td>≥2 or any COPD-related hospitalization</td>
</tr>
<tr>
<td>3</td>
<td>D</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>A</td>
<td>1 or less and not leading to hospitalization</td>
</tr>
<tr>
<td>1</td>
<td>B</td>
<td></td>
</tr>
</tbody>
</table>

CAT <10 or mMRC* 0-1 Few symptoms  
CAT≥10 or mMRC* ≥2 Many symptoms

*mMRC Modified Medical Research Council

## 2017 GOLD Guidelines Severity

<table>
<thead>
<tr>
<th>Exacerbations within the past 12 months</th>
<th>COPD Severity Group</th>
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</thead>
<tbody>
<tr>
<td>≥2 or any COPD-related hospitalization</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>D</td>
</tr>
<tr>
<td>1 or less and not leading to hospitalization</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>B</td>
</tr>
<tr>
<td>CAT &lt; 10 or mMRC* 0-1 Few symptoms</td>
<td></td>
</tr>
<tr>
<td>CAT ≥ 10 or mMRC* ≥ 2 Many symptoms</td>
<td></td>
</tr>
</tbody>
</table>

* mMRC modified Medical Research Council

1. Use SPIROMETRY to diagnose COPD and assess airflow limitation (GOLD grade)
2. Use CAT scale or mMRC to assess COPD symptoms
3. Determine the risk of exacerbations
   a. Identify the number of COPD exacerbations in the past 12 months
   b. Assess the number of COPD-related hospitalizations in the past year

Question 2: Which of the following types of medications are currently recommended for a 45-year-old with one COPD-related hospitalization in the past year, a CAT score of 28 and a FEV1 49% of the predicted value with no airway reversibility who is using an albuterol metered-dose inhaler (MDI) 90 mcg 2 puffs 3 to 4 times/day for COPD symptoms?

A. Tiotropium/Olodaterol
B. Budesonide/Formoterol
C. Fluticasone/Umeclidinium/Vilanterol
D. Ipratropium/Albuterol
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## 2016 GOLD Guidelines Initial Medication Recommendations

<table>
<thead>
<tr>
<th>GOLD Grade</th>
<th>COPD Severity Group</th>
<th>Exacerbations within the past 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>LAMA or ICS/LABA C</td>
<td>≥2 or any COPD-related hospitalization</td>
</tr>
<tr>
<td>3</td>
<td>LAMA +/− ICS/LABA D</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>SAMA or SABA A</td>
<td>1 or less and not leading to hospitalization</td>
</tr>
<tr>
<td>1</td>
<td>LAMA or LABA B</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CAT &lt;10 or mMRC* 0-1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Few symptoms</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CAT ≥10 or mMRC* ≥2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Many symptoms</td>
<td></td>
</tr>
</tbody>
</table>

*mMRC modified Medical Research Council*

## 2017 GOLD Guidelines Initial Medication Recommendations

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<th>COPD Severity Group</th>
</tr>
</thead>
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<tr>
<td>≥2 or any COPD-related hospitalization</td>
<td>LAMA C</td>
</tr>
<tr>
<td></td>
<td>LAMA+LABA D</td>
</tr>
<tr>
<td>1 or less and not leading to hospitalization</td>
<td>SAMA or SABA or LAMA or LABA A</td>
</tr>
<tr>
<td></td>
<td>CAT &lt;10 or mMRC* 0-1 Few symptoms</td>
</tr>
</tbody>
</table>

*CAT modified Medical Research Council*  
Question 3: 82-year-old with Gold grade 2, group D COPD was previously taking tiotropium/olodaterol and doing well. Her insurance no longer covers this medication. Which of the following medications would be appropriate to recommend?

- [A] Glycopyrrolate and formoterol
- [B] Fluticasone furoate and vilanterol
- [C] Budesonide and formoterol
- [D] Albuterol and ipratropium
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New COPD Pharmacotherapy Options
Goals of Treatment with Inhaler Emphasis

Reduce risk
- Prevent disease progression
- Prevent and treat exacerbations
- Reduce mortality

Reduce symptoms
- Relieve symptoms
- Improve exercise tolerance
- Improve health status

Personalized Plans
- Medication coverage
- Efficacy
- Safety
- Ease of use

Inhaler “Improvement”

• Facilitating drug delivery
  – Removing coordination of activation and inhalation
• Reducing the frequency
  – Multiple daily doses to once daily
• Minimizing the number of inhalers
  – Combining different medications into one inhaler
  – Minimizing the copayment
• However, still the same drug classes
# Comparison of LAMA

<table>
<thead>
<tr>
<th>Drug</th>
<th>Year Approved</th>
<th>Device</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tiotropium</td>
<td>2014</td>
<td>Respimat SMI*</td>
<td>5 mcg</td>
<td>Daily</td>
</tr>
<tr>
<td></td>
<td>2004</td>
<td>Handihaler DPI**</td>
<td>18 mcg</td>
<td>Daily</td>
</tr>
<tr>
<td>Aclidinium</td>
<td>2012</td>
<td>Pressair DPI</td>
<td>400 mcg</td>
<td>BID</td>
</tr>
<tr>
<td>Umeclidinium</td>
<td>2014</td>
<td>Ellipta DPI</td>
<td>62.5 mcg</td>
<td>Daily</td>
</tr>
<tr>
<td>Glycopyrrolate</td>
<td>2015</td>
<td>Neohaler DPI</td>
<td>15.6 mcg</td>
<td>BID</td>
</tr>
</tbody>
</table>

*SMI Soft-mist inhaler  ** DPI Dry-powder inhaler
## Comparison of LAMA Outcomes

<table>
<thead>
<tr>
<th>Drug</th>
<th>Evidence</th>
<th>Comparison with Tiotropium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tiotropium</td>
<td>-Prevents exacerbations and hospitalizations</td>
<td>Gold Standard</td>
</tr>
<tr>
<td></td>
<td>-Reduces symptoms</td>
<td></td>
</tr>
<tr>
<td>Aclidinium</td>
<td>-Prevents hospitalizations</td>
<td>No significant difference</td>
</tr>
<tr>
<td></td>
<td>-Reduces symptoms</td>
<td></td>
</tr>
<tr>
<td>Umeclidinium</td>
<td>-Reduces symptoms</td>
<td>Improved quality of life</td>
</tr>
<tr>
<td>Glycopyrrolate</td>
<td>-Prevents exacerbations and hospitalizations</td>
<td>Improved FEV1</td>
</tr>
<tr>
<td></td>
<td>-Reduces symptoms</td>
<td></td>
</tr>
</tbody>
</table>

# LAMA/LABA Combinations

<table>
<thead>
<tr>
<th></th>
<th>Umeclidinium and Vilanterol</th>
<th>Tiotropium and Olodaterol</th>
<th>Glycopyrrolate and Indacaterol</th>
<th>Glycopyrrolate and Formoterol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Device Year</strong></td>
<td>Ellipta DPI 2013</td>
<td>Respimat SMI 2016</td>
<td>Neohaler DPI 2016</td>
<td>Aerosphere MDI 2016</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>62.5 mcg/25 mcg 1 inhalation <strong>daily</strong></td>
<td>2.5 mcg/2.5 mcg 2 inhalations <strong>daily</strong></td>
<td>27.5 mcg/15.6 mcg 1 cap for inhalation twice daily</td>
<td>9 mcg/4.8 mcg 2 inhalations twice daily</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Improved FEV1, QOL and decreased albuterol use at 24 weeks.</td>
<td>Improved FEV1 at 52 weeks.</td>
<td>Improved FEV1 at 52 weeks. Improved QOL Decreased exacerbations</td>
<td>Improved FEV1, QOL and decreased albuterol use at 52 weeks</td>
</tr>
</tbody>
</table>

Question 4: A 55-year-old with COPD returns to clinic with questions about the proper use of his Respimat inhaler. Which of the following techniques is correct for use of this inhaler?

A. Priming the inhaler before the first use
B. Opening the cap and then twisting the base
C. Placing the mouthpiece 2 finger spaces away from the mouth
D. Inhaling using a quick, steady breath
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# Critical Errors with Inhalers

<table>
<thead>
<tr>
<th>Inhaler Type</th>
<th>COPD Critical Error Rate (%)</th>
<th>Ease of use (%) or preference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diskus</td>
<td>44-50</td>
<td>60</td>
</tr>
<tr>
<td>Ellipta</td>
<td>5-30</td>
<td>92-97</td>
</tr>
<tr>
<td>Handihaler</td>
<td>55-57</td>
<td>38</td>
</tr>
<tr>
<td>MDI</td>
<td>60-62</td>
<td>19.4-44</td>
</tr>
<tr>
<td>Neohaler (Breezhaler)</td>
<td>46-58</td>
<td>55</td>
</tr>
<tr>
<td>Respimat</td>
<td>n/a</td>
<td>80.6</td>
</tr>
<tr>
<td>Turbuhaler</td>
<td>44-58</td>
<td>55</td>
</tr>
</tbody>
</table>

Demonstration Inhalers

• www.use-inhalers.com
  – Non-branded web site
  – Multiple languages (Spanish, Polish, Mandarin...)
  – Subtitles
  – Inspiratory indicator
  – Patient instruction handouts
Question 5: Which of the following step-up options is recommended for a 75-year-old woman with GOLD grade 4, group D COPD currently taking ICS/LABA and a LAMA?

She is adherent to her inhalers and is able to use them correctly.
She is on 2L oxygen/24 hours.
She continues to have a CAT score of 30 and a COPD exacerbation every other month. Despite quitting smoking 1 year ago, she is losing weight and complains feeling depressed.

A. Azithromycin
B. Roflumilast
C. Theophylline
D. Prednisone
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Step-up or Alternative Medication Recommendations

• 2016
  – LAMA and/or LABA and or ICS combinations
  – SAMA and SABA
  – Theophylline
  – Roflumilast and LAMA
  – Roflumilast and LABA
  – ICS and LABA and roflumilast

• 2017
  – LAMA and/or LABA combination
  – LABA and ICS
  – LAMA+LABA+ICS
  – Step-up
    – Roflumilast
    – Azithromycin
    – Erythromycin
  – Other
    – ICS withdrawal

ICS and LAMA and LABA

• Fluticasone furoate and umeclidinium and vilanterol 100 mcg /62.5 mcg/25 mcg Ellipta daily
• Approved by FDA September 2017
  – Improved FEV1 compared with ICS/LABA
  – Significant improvement in QOL
  – 35% reduction in moderate/severe exacerbations (95% CI, 14-51; p=0.002)

Azithromycin and Erythromycin

- Decrease exacerbations when used for 6-12 months
- No significant decrease in hospitalizations or mortality
- Increased side effects
- Unknown:
  - Optimal dosing
  - Duration of therapy
  - Subpopulation with benefit

Best Practices in Optimal COPD Management
Question 6: Which of the following is true concerning smoking cessation and COPD?

- **A** Stopping smoking decreases mortality
- **B** Varenicline is associated with greater psychiatric adverse events than nicotine replacement therapy (NRT) patches
- **C** NRT patches are more effective than varenicline for smoking cessation
- **D** A low-dose CT scan is not recommended for lung cancer screening if the patient quit smoking in the past year
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Tobacco Dependence Treatment

- Single most effective and cost-effective intervention
- Per SUMMIT trial 47% of COPD patients are current smokers
  - GOLD grade 2, group B and D
- 18% all-cause mortality reduction in the smoking cessation group of the Lung Health Study
- As pharmacists are we forgetting this step?

The Evaluating Adverse Events in Global Smoking Cessation Study (EAGLES)

<table>
<thead>
<tr>
<th>Design</th>
<th>Randomized, double-blind, triple-dummy, placebo-controlled, active-controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Setting</td>
<td>140 centers, 16 countries, 5 continents</td>
</tr>
<tr>
<td>Primary Objective</td>
<td>Compare the relative safety and efficacy of varenicline, bupropion, nicotine replacement</td>
</tr>
<tr>
<td>Randomization</td>
<td>Varenicline 1 mg orally twice daily, bupropion SR 150 mg orally twice daily, NRT patch 21 mg daily with taper or placebo</td>
</tr>
<tr>
<td>Participants</td>
<td>Psychiatric (n=4116) and non-psychiatric cohort (n=4028)</td>
</tr>
</tbody>
</table>

Safety of Tobacco Treatment Medications

Neuropsychiatric Adverse Events

- NRT patch: 3.90%
- Bupropion: 4.50%
- Varenicline: 4.00%
- Placebo: 3.70%

Effectiveness of Tobacco Dependence Medications

Abstinence Rates Weeks 9-24

- NRT patch: 15.7%
- Bupropion: 16.2%
- Varenicline: 21.8%
- Placebo: 9.4%

## The Evaluating Adverse Events in Global Smoking Cessation Study (EAGLES)

<table>
<thead>
<tr>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled only if smoked 10 or more cigarettes/day</td>
</tr>
<tr>
<td>Alcohol and other drug use disorders excluded</td>
</tr>
<tr>
<td>Stable psychiatric condition (no exacerbation in the past 6 months or medication changes in 3 months)</td>
</tr>
<tr>
<td>Severe COPD excluded</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>No significant increase in neuropsychiatric adverse events from active treatment vs. placebo</td>
</tr>
<tr>
<td>Varenicline more effective for achieving abstinence than other active treatments and placebo</td>
</tr>
<tr>
<td>Bupropion and NRT patch more effective for achieving abstinence than placebo</td>
</tr>
</tbody>
</table>

Are medications causing more harm than good?

Low-Dose Chest Computed Tomography

- **Screening**
  - 55-80 years of age
  - Current smoker or quit within the previous 15 years
  - 30 pack-year or longer history

- **Improved survival from lung cancer**
- **Opportunity to discuss smoking cessation treatments**

U.S. Preventive Services Task Force

Key Takeaways

• Key Takeaway #1
  – COPD severity classification takes into account symptoms along with exacerbations and hospitalizations

• Key Takeaway #2
  – Personalized care should be provided when selecting a COPD inhaler

• Key Takeaway #3
  – Smoking cessation is still the most effective, life-saving intervention for COPD
Chronic Obstructive Pulmonary Disease: New Approaches to an Old Problem

Dennis Williams, Pharm.D., BCPS, AE-C
Associate Professor and Vice-Chair, Division of Pharmacotherapy and Experimental Therapeutics
University of North Carolina Eshelman School of Pharmacy
Chapel Hill, North Carolina
Question 7: A patient is newly diagnosed with COPD based on medical history and spirometry. Which of the following parameters would be used to assign a severity category for this patient?

A. Forced Vital Capacity (FVC) on spirometry
B. Standardized Six-Minute Walk distance
C. Number of exacerbations within the past year
D. Oxygen level from arterial blood gas (pO₂)
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Question 8: A COPD patient reports a history of intolerance to propellants in inhalers. Which of the following inhalation delivery systems uses a propellant?

A. Metered-dose inhaler
B. Dry powder inhaler
C. Jet nebulizer
D. Propellants are no longer used in inhalation devices
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Question 9: In selecting a medication for a COPD patient who has continued to experience frequent symptoms despite albuterol use, which of the following therapies has been proven to modify the natural course of COPD (e.g., decline in Forced Expiratory Volume in one second [FEV₁])?

A. Long-acting beta₂ agonists  
B. Long-acting anticholinergics  
C. Inhaled corticosteroids (ICS)  
D. No therapy has been shown to impact the natural course of COPD
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Evidence Supporting a Clinical Guideline Approach to COPD Management
FLAME Study

Indacaterol-Glycopyrronium (long-acting beta₂ agonist [LABA]/long-acting antimuscarinic antagonist [LAMA] versus Salmeterol-Fluticasone (LABA/inhaled corticosteroid [ICS]) for COPD

Methods

• 52-week, randomized, double-blind, double-dummy, noninferiority trial
  – Noninferiority margin designated as 15%
• Study Population: COPD patients with ≥1 exacerbation in previous year
• Tx Groups: Inhaled regimen
  – Indacaterol 110 mcg/Glycopyrronium 50 mcg once daily vs. Salmeterol 50 mcg/Fluticasone 500 mcg twice daily
• Primary Outcome: Annual rate of all COPD exacerbations
• 27 secondary outcomes were evaluated, including time to first exacerbation

Study Subject Characteristics

• n=3362; treatment groups appeared similar

• Typical subject:
  – 65 year old male (76% male)
  – COPD for mean of 7.3 years, with Group D severity (74.8%)
  – Receiving ICS at screening (56.3%)
  – FEV$_1$ of 1.2L (44.1% Predicted)

Results

FLAME Study

"Indacaterol–Glycopyrronium versus Salmeterol–Fluticasone for COPD"

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Results

- Annual exacerbation rate 11% lower with LABA/LAMA compared to LABA/ICS
  - 3.59 vs 4.03; NNT=228
- Time to first exacerbation of any severity was lower with LABA/LAMA vs. LABA/ICS
- Incidence for adverse events was similar in both groups, except for pneumonia which was lower with LABA/LAMA (3.2% vs 4.8%; p=0.02)

Assessment of Study Limitations

• Included mild exacerbations (worsening of symptoms for >2 days with no change in therapy) in total outcome measure
• Once daily (LABA/LAMA) vs. Twice daily (LABA/ICS) regimens studied
• Some subjects in LABA/LAMA group received LABA/ICS prior to enrollment
• Indacaterol/Glycopyrronium product differed from product available in U.S.

FULFIL Study

Once-Daily Triple Therapy (LABA/LAMA/ICS) for Patients with COPD

Methods

• 24-week randomized, double-blind, double-dummy study

• Two treatment groups
  – Fluticasone furoate (FF)/umeclidinium (UMEC)/vilanterol (VI) 100mcg/62.5mcg/25mcg
  – Budesonide (BUD)/formoterol (FOR) 400mcg/12mcg

• Co-primary endpoints
  – Change from baseline in FEV$_1$
  – St. George’s Respiratory Questionnaire (SGRQ)

Study Subject Characteristics

- n=1810
- Typical subject:
  - 64-year-old male (74%)
  - Current or former smoker with 39 pack-year history
  - FEV$_1$ of 1.34L (45% predicted)
  - Experienced $\geq$ 1 moderate or severe exacerbation in past year (65%)

Results: Change in Baseline FEV$_1$

The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society.
Results

• Intention-to-treat analysis
• Mean change in FEV$_1$ of 142mL (with FF/UMEC/VI) vs. (-)29mL (with BUD/FOR); p<0.001
• Mean decrease in SGRQ score of 6.6 units and 4.3 units, respectively; p<0.001
• Secondary outcome:
  – 35% reduction in exacerbation rate with triple therapy (LABA/LAMA/ICS)
• Adverse event rates similar in the two groups, including pneumonia (~1.9%) and cardiovascular (CV) events (~10%)

Assessment of Study Limitations

- Once daily LABA/LAMA/ICS therapy compared to twice daily LABA/ICS
- Short duration of study
- Clinical relevance of FEV$_1$ improvement is uncertain
- COPD Exacerbation rate would be more clinically meaningful outcome

WISDOM Study
Withdrawal of Inhaled Corticosteroids and Exacerbations of COPD

Methods

• 12-month, double-blind, parallel-group study
  – Median time to first primary event assumed to be 9 months
  – Noninferiority margin for Hazard Ratio (HR) set at 1.2

• 6-week run-in with triple therapy
  – tiotropium, salmeterol, fluticasone propionate

• ICS (fluticasone) withdrawn in intervention group
  – Three steps over 12 weeks

• Primary outcome:
  – Time to first moderate/severe exacerbation

Study Subject Characteristics

• 2485 Subjects randomized; no significant differences between tx groups

• Typical subject:
  – 64-year-old male (82.5% male)
  – COPD for mean of 7.87 years, with FEV1 <50% (99.3%)
  – FEV$_1$ of 0.98L (34.2% Predicted)
  – Receiving ICS at screening (69.9%)

• 39% of subjects were receiving triple therapy at enrollment prior to 6-week run-in

Results

WISDOM Study*

*IGC is designation for ICS

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Results
WISDOM Study

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Results
WISDOM Study

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Results

• HR for time to first moderate or severe exacerbation was 1.06 (0.94-1.19); noninferiority claim met
• COPD exacerbation occurred in first 25% of subjects at ~108 days
• HR for time to severe exacerbation (secondary outcome) was 1.20 (0.98-1.48)
• Incidence of pneumonia did not differ significantly between groups (5.5% and 5.8%)
• Decline in FEV₁ was 43 mL greater in ICS discontinuation vs. continuation arm

Assessment of Study Limitations

• Study population was largely male and Caucasian
• Therapies administered in separate inhalers (3)
• Started with high-dose fluticasone (1 mg daily)
• Status of subjects at time of intervention not clearly reported

RE²SPOND Trial

Phosphodiesterase (PDE)-4 Inhibitor Added to Double or Triple Inhaled Therapy

Question 10: The primary outcome in the roflumilast RE²SPOND trial was the effect on

- **A** Improvements in FEV$_1$
- **B** Survival in COPD patients
- **C** Rate of moderate or severe COPD exacerbations
- **D** Rate of hospitalization from COPD exacerbations
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Methods

• 52-week, multicenter, randomized, double-blind, placebo-controlled trial

• Roflumilast added to either:
  – ICS/LABA (53% of subjects)
  – ICS/LABA/LAMA (47% of subjects)

• Primary outcome
  – Rate of moderate or severe exacerbations

Study Subject Characteristics

- 2352 subjects randomized
- Typical subject:
  - 64 years old
  - Male (79%)
  - Caucasian (79%)
  - Severe or very severe (based on FEV$_1$) COPD (99%) for mean of 9.2 years
  - FEV$_1$ of 0.98L (33% predicted)
  - 2.4 moderate or severe exacerbations in past 12 months

Results

• Annual exacerbation rate was 1.17 for roflumilast group and 1.27 for control group
  – RR 0.92 (0.81-1.04); p=0.163
• Approximately 50% of subjects experienced 0 exacerbations and ~27% had one
• Exacerbation rate was reduced in subgroup with >3 exacerbations
  – From 2.62 to 1.59 (p=0.03)
• Discontinuation of therapy due to adverse events: 11.7% with roflumilast and 5.4% with placebo (diarrhea 10%, weight loss 8%)

Assessment of Study Limitations

• Failed to meet primary endpoint
• Excluded subjects receiving high dose ICS with LABA
• Originally excluded subjects receiving LAMA until study revision
• Observations regarding benefits in subjects with >3 exacerbations, or who experienced severe exacerbation in the past, were made during post-hoc analysis

Considerations Regarding Role of Roflumilast

- Inhaled therapy should be optimized prior to considering additional agents to reduce exacerbation risks.
- Roflumilast may be beneficial when added to double or triple inhaled therapy for patients with a history of frequent exacerbations (>3) or exacerbations requiring hospitalization.
- Patients should be monitored for possible GI and psychiatric adverse effects, which have been reported in other studies.
Question 11: In evaluating the medication regimen for a COPD patient, which of the following agents would not be expected to be used as a single chronic therapy?

- A. Long-acting inhaled beta$_2$ agonists
- B. Long-acting inhaled anticholinergics
- C. Short-acting inhaled anticholinergics
- D. Inhaled corticosteroids
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Impact of Using Multiple Inhalers with Different Inhalation Techniques on COPD Outcomes

Impact of Using Multiple Inhalers with Different Inhalation Techniques on COPD Outcomes

• Matched cohort design using patient care research database in Australia

• Included 8225 subjects in each of two cohorts: Similar devices or mixed devices
  – Dry-powder inhalers (DPIs) and/or metered-dose inhalers (MDIs)

• Subjects followed for 2 years between 2008 and 2015

• Primary outcome: Incidence Rate Ratio (IRR) of moderate or severe exacerbation rates

Impact of Using Multiple Inhalers with Different Inhalation Techniques on COPD Outcomes

• Subjects in sample
  – Mean age 67 years
    – 71.3% between 61 and 80 years
  – Male (56.5%)
  – Smoker (36.8%)
  – Mean baseline FEV$_1$ 56%

## Results

<table>
<thead>
<tr>
<th></th>
<th>Similar Devices Cohort</th>
<th>Mixed Devices Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of Exacerbations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>58.5%</td>
<td>53.4%</td>
</tr>
<tr>
<td>1-2</td>
<td>34.2%</td>
<td>36.1%</td>
</tr>
<tr>
<td>≥ 3</td>
<td>7.3%</td>
<td>10.6%</td>
</tr>
<tr>
<td><strong>Daily short-acting beta₂ agonist (SABA)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dose (mcg)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-110</td>
<td>38.7%</td>
<td>27%</td>
</tr>
<tr>
<td>111-550</td>
<td>42.4%</td>
<td>46.6%</td>
</tr>
<tr>
<td>&gt;550</td>
<td>18.9%</td>
<td>26.4%</td>
</tr>
</tbody>
</table>

Results

• Similar device use associated with lower risk for exacerbations
  – IRR 0.82 (0.80-0.84)

• Similar device use associated with ~50% of SABA (albuterol) use compared with mixed device use
  – OR 0.54 (0.51-0.57)

Conclusions

• Both MDIs and DPIs present challenges (to users)
• Patients using inhalers with different technologies and inhalation techniques are at risk for worse outcomes than patients using inhalers with the same technique
  – Increased exacerbation risk
  – Increased SABA requirements
• Consideration should be given to selecting inhalers with similar techniques when prescribing inhaled medications

Best Practices in Optimal COPD Management
Question 12: Annual COPD exacerbation rates decreased from 20% to 15% following the introduction of a new therapy. Which of the following is the Number Needed To Treat (NNT) for one year to prevent one additional exacerbation?

A 15
B 20
C 50
D 100
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Global Initiative for Chronic Obstructive Lung Disease (GOLD) Global
Strategy for the Diagnosis, Management, and Prevention of COPD

Treatment Goals: 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 Side Effects

Medication Principles for Optimal COPD Management

• Bronchodilators are the focus of pharmacotherapy
• No medication has been shown to slow the natural progression of COPD
• Long-acting bronchodilators are more effective and convenient for patients with chronic symptoms
• LAMAs are more effective at reducing exacerbation risk and hospitalizations
Question 13: Which of the following therapies can increase the risk of pneumonia in patients with COPD?

- A. Inhaled corticosteroids
- B. PDE-4 inhibitors
- C. Long-acting beta agonists
- D. Long-acting anticholinergics
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Question 14: Which of the following spirometric parameters is most appropriate to monitor in patients with COPD?

A. Peak expiratory flow rate
B. Pre-bronchodilator force expiratory volume in one second (FEV₁)
C. Forced vital capacity (FVC)
D. Post-bronchodilator forced expiratory volume in one second (FEV₁)
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Optimal Management Strategies for Patients with COPD

- Trigger avoidance
  - Particularly environmental/occupational exposures, including cigarette smoke
- Smoking cessation support
- Vaccinations
  - Pneumococcal vaccine
  - Influenza vaccine
- Pulmonary rehabilitation (depending on severity)
- Supplemental oxygen therapy when indicated

Self-Management Education

- Basic understanding of COPD
- Approach to treatment
- Smoking cessation
- Strategies to minimize dyspnea
- When to seek help
- Strategies for managing exacerbations
- Advanced directives

Standardized Strategies for Tobacco Cessation Counseling

- Ask
- Advise
- Assess
- Assist
- Arrange

Question 15: Which of the following strategies involving 23-valent pneumococcal polysaccharide vaccine (PPSV23) and/or 13-valent pneumococcal conjugate vaccine (PCV13) is recommended for a 55-year-old patient with COPD?

A. Administer PPSV23 and PCV13 now
B. Administer PPSV23 now without PCV13
C. Administer PCV13 now and PPSV23 in 8 weeks
D. Administer PCV13 now without PPSV23
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Question 16: An investigator predicted that a proposed campaign for pneumococcal vaccination would reduce the annual incidence of invasive pneumococcal disease from 24% in unvaccinated people to 10% in vaccinated people. What is the absolute risk reduction for invasive pneumococcal disease associated with this prediction?

A 14%
B 24%
C 58%
D 220%
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Value-Based Purchasing Considerations

• Health systems are penalized for readmissions
• In 2008, 30-day readmission with primary diagnosis of COPD was 7.1%; the rate with any COPD diagnosis was 17.3%
• Overall, COPD associated with a 20.5% 30-day readmission rate
• Costs for readmission higher than for initial stays
  – $8400 vs. $7100

Reducing Hospital Readmission Rates

• Pre-Post Observational Analysis at academic medical center
• Pharmacists provided medication reconciliation and discharge education (the intervention)
• Primary outcome:
  – Composite of readmission or return to emergency department within 30 days

Results

• 3316 patients included as subjects during study
  – Completion rate for medication reconciliation was 95.8% at admission and 69.7% at discharge

• Results were not statistically significant (NS) for primary outcome

• For high-risk patients (COPD, heart failure (CHF), pneumonia, acute myocardial infarction (AMI), anticoagulation), 30-day readmissions decreased from 17.8% to 12.3% (p=0.042)

• Cost savings estimated at $780K annually

Reducing Hospital Readmissions

- Retrospective analysis based on chart review
- Pharmacist conducted medication reconciliation for COPD discharges during 1-month period in 2012
- 29 patients received intervention; 30-day readmission rate decreased from 22.2% to 16.0%
- Investigator proposed that additional benefit is possible with greater investment, including patient education and counseling, monitoring and encouraging adherence, and ensuring access to medications

Benefit of Early and Timely Follow Up

- Systematic review of studies involving patients discharged with heart failure or COPD
- Review included one randomized controlled trial (RCT), two uncontrolled trials, and seven observational studies
- Typical intervention was a follow up provided by generalist/specialist physician, nurse, or pharmacist
- Interventions included clinic visit, telephone call, or home visit
- Concluded that intervention within 7 to 30 days after hospital discharge associated with reduced risk for readmission

Strategies to Minimize Risks for Readmission

- Use COPD guideline-directed protocols in emergency departments and hospital
- Provide patient and caregiver education on smoking cessation, proper inhaler use and action plans for acute exacerbations
- Assess supplemental oxygen requirements, comorbidities, goals of care and spirometry results
- Provide a follow-up plan that includes a medical provider visit within 7-10 days, post-discharge phone call at 48-72 hours, pulmonary rehabilitation services when available and appropriate home care resources

Care Following Hospital Discharge

• Ensure smooth transition
  – Medication changes, access, inhaler technique, self-management plan, and general understanding

• Follow-up clinic visit within 1 to 4 weeks
  – Review medication regimen, inhaler technique
  – Assess symptoms and ability to perform activities of daily living; evaluate comorbidities

• Follow-up clinic visit within 12 to 16 weeks
  – Repeat 1 to 4 week assessments and perform spirometry

Periodic Assessment Parameters for COPD

• Adherence
• Inhaler technique
• Avoidance of triggers
• Presence and control of comorbidities
• Vaccine status
Key Takeaways

• Key Takeaway #1
  – Dual bronchodilator therapy is a new strategy for managing COPD with the benefit of reserving ICS therapy for patients at highest risk for exacerbations

• Key Takeaway #2
  – De-escalation of pharmacotherapy in COPD is an emerging concept with potential therapeutic, safety, and economic benefits

• Key Takeaway #3
  – Transition of care strategies are effective for reducing hospital readmissions and improving overall outcomes for COPD patients
Questions?