Session 6: Evolving Therapeutic Approaches in the Clinical Management of COPD

Learning Objectives

1. Identify key pathophysiological features that define chronic obstructive pulmonary disease (COPD) based on current clinical guidelines
2. Describe classic patient characteristics and clinical presentation qualities associated with COPD
3. Discuss the current treatment paradigm as it relates to long-acting bronchodilators for the management of chronic obstructive pulmonary disease
4. Develop effective disease and treatment management strategies for the long term care of patients with COPD
5. Evaluate emerging data on novel, long acting β2-agonist and muscarinic therapies for COPD and appropriately integrate them in individual treatment plans

Faculty

Mark Avdalovic, MD, MAS, FCCP
Assistant Clinical Professor
University of California, Davis Medical Center
Sacramento, California

Dr Mark Avdalovic is an assistant clinical professor at the University of California, Davis Medical Center in Sacramento, California. He graduated from the Medical College of Wisconsin in 1996 and completed his internal medicine residency and pulmonary and critical care fellowship at the University of California, Davis Medical Center. Dr Avdalovic’s areas of clinical interest include COPD and pulmonary hypertension. He uses a unique animal model of COPD to study the mechanism of vascular remodeling in the lung as part of wound healing and repair. In addition to his clinical and basic science work, Dr Avdalovic is also very active in the clinical and research applications of the electronic health record and has recently begun work to develop a comprehensive registry of COPD patients from the UC Davis Health System. Dr Avdalovic has authored and coauthored publications and spoken at major conferences on COPD.

Raul Mendoza, MD, FCCP
Director, Intensive Care Unit and Respiratory Care
Aurora BayCare Medical Center
Green Bay, Wisconsin

Dr Raul Mendoza is the director for the intensive care unit and respiratory care at Aurora BayCare Medical Center, Green Bay, WI. He is also a clinical assistant professor at the University of Wisconsin School of Medicine and Public Health. His main interest is in clinical pulmonary medicine including obstructive lung disease, sarcoidosis, and lung cancer. Dr Mendoza graduated from medical school at Anahuac University, Mexico City, in 1991.

He completed his residence in internal medicine and pulmonary fellowship at the University of Miami/Jackson Memorial Hospital in 1998 and was designated chief fellow during his last year. Dr Mendoza has participated in basic research and clinical trials which have included the use of ultra low molecular weight heparin to prevent bronchospasm in allergic sheep. He has also participated in clinical trials for COPD and sarcoidosis. Dr Mendoza has authored and coauthored publications and spoken at major conferences over the past 12 years.
**Faculty Financial Disclosure Statements**

The presenting faculty reports the following:

Mark Avdalovic, MD, MAS, FCCP, reported a financial interest/relationship or affiliation in the form of: Research funding from National Institutes of Health (NIH), Merck & Co. Inc., and Novartis Pharmaceuticals Corporation; consulting fees from Novartis Pharmaceuticals Corporation and Bayer Pharmaceuticals Corporation.

Raul Mendoza, MD, FCCP, reported a financial interest/relationship or affiliation in the form of: Honoraria, Forest Pharmaceuticals, Inc.

**Education Partner Financial Disclosure Statement**

The content collaborators at AXIS Medical Education report the following:

Linda King, MS, and Diedrea White, BA, have no financial relationships to disclose.

**Suggested Reading List**


Decramer M, Wedzicha JA, Ficker J, et al. Once-daily QVA149 improves health-related quality of life in patients with severe to very severe COPD: the SPARK study. [ATS abstract 40786; Session C45; Date: May 21, 2013 Time: 10:45-12:30].

Decramer M, Wedzicha JA, Sandstrom T, et al. Safety and tolerability of QVA149, glycopyrronium and tiotropium in patients with severe to very severe COPD: the SPARK study. [ATS abstract 41616; Session A43; Date: May 19, 2013 Time: 10:45-12:30].


Mahler DA, Decramer M, D'Urzo AD, et al. Superior Lung Function With Once-Daily Qva149 Translates Into Improvements In Patient-Reported Breathlessness Compared With Placebo And Tiotropium In COPD Patients: The Blaze Study. [ATS abstract 45308; Session C20; Date: May 21, 2013 Time: 8:15-10:45].


Evolving Therapeutic Approaches in the Clinical Management of COPD

SPEAKERS
Mark Avdalovic, MD, MAS, FCCP
Raul Mendoza, MD, FCCP

SESSION 6
3:45–5pm

Presenter Disclosure Information

Off-Label/Investigational Discussion

► In accordance with pmICME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

Evolving Therapeutic Approaches in the Clinical Management of COPD

Mark Avdalovic MD, MCSc
Associate Professor of Clinical Medicine
UC Davis Medical Center – Sacramento, CA

Raul Mendoza, MD, FCCP
Pulmonary Physician
Aurora Medical Group – Green Bay, WI

Drug List

glycopyrrolonium bromide
tiotropium bromide
beclomethasone dipropionate
tiotropium bromide
budesonide
tioconazole
fluticasone propionate
salmeterol
fenoterol
tuloxytropium bromide
beclomethasone
timolol maleate
levalbuterol tartrate
salmeterol
albuterol sulfate
vedrotide
formoterol fumarate
indacaterol
tulobuterol
tiaclidinium bromide
QVA149
GSK233705
NVA237
AZD9164

Learning Objectives

Upon completion of this activity, participants should be better able to:

o Identify key pathophysiological features that define chronic obstructive pulmonary disease based on current clinical guidelines
o Describe classic patient characteristics and clinical presentation qualities associated with COPD
o Discuss the current treatment paradigm as it relates to long-acting bronchodilators for the management of chronic obstructive pulmonary disease
o Develop effective disease- and treatment-management strategies for the long-term care of patients with COPD
o Evaluate emerging data on novel, long-acting β2-agonist and muscarinic therapies for COPD and appropriately integrate them in individual treatment plans
Activity Agenda: Part 1

- Introduction – 5 mins
- Pinpointing and Diagnosing Chronic Obstructive Pulmonary Disease – 30 mins
  - Epidemiologic overview
  - COPD pathogenesis
  - Bronchial and emphysematous phenotypes
  - Significant patient characteristics and clinical presentation
  - Pulmonary diagnostics
  - Common management strategies
  - Case Study No. 1

Activity Agenda: Part 2

- Current and Future Management of COPD – 30 mins
  - Update on the 2013 GOLD clinical guidelines
  - Standard treatment options
  - Preferred usage of long-acting bronchodilators
  - Emerging treatments and regimens
  - Case Study No. 2
  - Future directions in the management of COPD

Pinpointing and Diagnosing Chronic Obstructive Pulmonary Disease

Mark Avdalovic MD, MCSc
Associate Professor of Clinical Medicine
UC Davis Medical Center – Sacramento, CA

COPD Definition

- Spirometry documented airflow limitation where the ratio of FEV1/FVC < 0.7 incompletely reversible with bronchodilator
- The presence of respiratory symptoms including cough, shortness of breath, sputum production and/or wheezing
- History of smoking (>10 pack years)

Epidemiologic Overview

- In the last five years, COPD became the third leading cause of death in the United States
- COPD has been diagnosed in close to 13 million Americans, with almost as many undiagnosed
- The overall cost of taking care of COPD patients including morbidity and mortality was close to $50 billion in 2010

COPD Pathogenesis

- Smoking is the number one cause of COPD
- Groups at higher risk from smoking
  - A-1 antitrypsin deficiency
  - Poor nutrition (eating disorders)
  - Premature birth
COPD Phenotypes

- Frequent exacerbations
- Air trapping-emphysema
- Airway hyper-responsiveness
- Co-morbidities

Chest X-Ray: Mild hyperinflation

Pulmonary Diagnostics

- Spirometry- REQUIRED!
- Chest radiography (CXR)
- Assessment of symptoms
  - MMRC or COPD Assessment Test (CAT)
- Exercise capacity
  - Six-minute walk

New Face of COPD

- As of 2003, women have higher prevalence of chronic bronchitis and emphysema and airflow limitation
- Airway hyper-responsiveness and centrilobular emphysema more common in women
- Greater dyspnea, symptoms and anxiety

General Management Strategies

- Smoking cessation
- Bronchodilator for symptomatic airflow limitation
- Vaccination
- Pulmonary rehabilitation (FEV1<50%)
- Oxygen therapy (PaO2<55mmHg, SaO2 <88%)
- Co-morbidities
  - Cardiovascular (heart failure, cardiovascular disease, peripheral artery disease)
  - Osteoporosis
  - Depression/anxiety
  - Cancer

FEV1 = Forced expiratory volume in 1 second
PaO2 = Partial pressure of oxygen in arterial blood
SaO2 = Saturation level of oxygen in hemoglobin

Case Study No. 1

77-year-old male clinically diagnosed COPD with progressive dyspnea. Patient reports a 40 pack/year smoking history, quit seven years ago. Coronary artery bypass grafting seven years ago. He reports dyspnea at rest and with exertion.

Physical exam:
- Inspiratory and expiratory wheezing, S4 gallop, 1-2+edema

Pulmonary Function Test
- FEV1/FVC :0.63
- FEV1: 1.41 (52%)
- FVC: 2.25 (60%)

FEV1 = Forced expiratory volume in 1 second
PaO2 = Partial pressure of oxygen in arterial blood
SaO2 = Saturation level of oxygen in hemoglobin
Case Study No. 1 (cont’d.)

- Initially started on tiotropium
- After 4 weeks minimal improvement
- Aggressively diuresed and afterload reduced (24lbs weight loss)

<table>
<thead>
<tr>
<th>Six Months</th>
<th>6 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstructive FEV1/FVC: 0.63</td>
<td>0.61</td>
</tr>
<tr>
<td>FEV1: 1.41 (52%)</td>
<td>2.10 (77%)</td>
</tr>
<tr>
<td>FVC: 2.25 (60%)</td>
<td>3.46 (92%)</td>
</tr>
<tr>
<td>FEF25-75: 0.71 (36%)</td>
<td>0.73 (37%)</td>
</tr>
<tr>
<td>TLC: 4.25L (68%)</td>
<td>5.17L (82%)</td>
</tr>
<tr>
<td>DlCO: 10.1 (42%)</td>
<td>10.6 (44%)</td>
</tr>
</tbody>
</table>

Summary

- Spirometry must be performed to establish a COPD diagnosis
- Women have a higher prevalence of COPD compared to men
- COPD is very heterogenous
- Common co-morbid diseases include heart failure, coronary heart disease, osteoporosis, depression/anxiety

Current and Future Management of COPD

Raul Mendoza, MD, FCCP
Pulmonary Physician
Aurora Medical Group – Green Bay, WI

Update on the 2013 GOLD Clinical Guidelines

- Effective management aimed to reduce symptoms and reduce risk:
  - Relieve symptoms
  - Improve exercise tolerance
  - Improve health status
  - Prevent disease progression
  - Prevent and treat exacerbations
  - Reduce mortality

Global Strategy for Diagnosis, Management and Prevention of COPD Therapeutic Options:

Key Points

- Smoking cessation has the greatest capacity to influence the natural history of COPD. Health care providers should encourage all patients who smoke to quit
- Pharmacotherapy and nicotine replacement reliably increase long-term smoking abstinence rates
- All COPD patients benefit from regular physical activity and should repeatedly be encouraged to remain active

Global Strategy for Diagnosis, Management and Prevention of COPD Therapeutic Options:

Key Points

- Appropriate pharmacologic therapy can reduce COPD symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance
- None of the existing medications for COPD has been shown conclusively to modify the long-term decline in lung function
- Influenza and pneumococcal vaccination should be offered depending on local guidelines
Bronchodilator medications are central to the symptomatic management of COPD. Bronchodilators are prescribed on an as-needed or on a regular basis to prevent or reduce symptoms. The principal bronchodilator treatments are beta2-agonists, anticholinergics, theophylline or combination therapy. The choice of treatment depends on the availability of medications and each patient’s individual response in terms of symptom relief and side effects.

Global Strategy for Diagnosis, Management and Prevention of COPD Therapeutic Options: Bronchodilators

- Bronchodilator medications are central to the symptomatic management of COPD.
- Bronchodilators are prescribed on an as-needed or on a regular basis to prevent or reduce symptoms.
- The principal bronchodilator treatments are beta2-agonists, anticholinergics, theophylline or combination therapy.
- The choice of treatment depends on the availability of medications and each patient’s individual response in terms of symptom relief and side effects.

Standard Treatment Options: Bronchodilators

**Bronchodilators (Short-Acting Beta-2 Agonists)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Inhaler (microgram)</th>
<th>Solution for nebulizer (mg/ml)</th>
<th>Oral</th>
<th>Vials for injection (mg)</th>
<th>Duration of action (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fenoterol</td>
<td>100-200 (MDI)</td>
<td>1</td>
<td>0.05% syrup</td>
<td>4-6</td>
<td></td>
</tr>
<tr>
<td>Levalbuterol</td>
<td>25-50 MDI</td>
<td>0.21, 0.42</td>
<td>5</td>
<td>0.024% syrup</td>
<td>6-8</td>
</tr>
<tr>
<td>Albuterol</td>
<td>100-200 MDI,DPI</td>
<td>5</td>
<td>5 mg pill</td>
<td>0.1-0.5</td>
<td>4-6</td>
</tr>
<tr>
<td>Terbutaline</td>
<td>400-500 DPI</td>
<td>2.5, 5 mg pill</td>
<td>4-6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MDI = Metered dose inhaler
DPI = Dry powder inhaler

Global Strategy for Diagnosis, Management and Prevention of COPD Therapeutic Options: Bronchodilators

**Bronchodilators (Long-Acting Beta-2 Agonists)**

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<tr>
<th>Drug</th>
<th>Inhaler (microgram)</th>
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<th>Duration of action (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formoterol</td>
<td>4.5-12 (MDI, DPI)</td>
<td>0.01</td>
<td>0.01</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Arformoterol</td>
<td>0.0075</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indacaterol</td>
<td>75-300 (DPI)</td>
<td>0.02</td>
<td>0.02</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Salmeterol</td>
<td>25-50 (MDI, DPI)</td>
<td>0.02</td>
<td>0.02</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Tulobuterol</td>
<td>2 mg (Transdermal)</td>
<td>24</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


**Standard Treatment Options: Bronchodilators (Long-Acting Beta-2 Agonists)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Inhaler (microgram)</th>
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<td>Terbutaline</td>
<td>400-500 DPI</td>
<td>2.5, 5 mg pill</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

MDI = Metered dose inhaler
DPI = Dry powder inhaler


**Bronchodilators (Long-Acting Anti-Cholinergics)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Inhaler (Microgram)</th>
<th>Duration of action (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipratropium bromide</td>
<td>20-40 (MDI)</td>
<td>6-8</td>
</tr>
<tr>
<td>Oxitropium bromide</td>
<td>100 (MDI)</td>
<td>7-9</td>
</tr>
</tbody>
</table>


**Global Strategy for Diagnosis, Management and Prevention of COPD Therapeutic Options: Bronchodilators**

- Long-acting inhaled bronchodilators are more effective for symptom relief than short-acting bronchodilators.
- Long-acting inhaled bronchodilators reduce exacerbations and related hospitalizations and improve symptoms and health status.
- Combining bronchodilators of different pharmacological classes may improve efficacy and decrease the risk of side effects compared to increasing the dose of a single bronchodilator.

Standard Treatment Options: Anti-Inflammatories

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose microgram</th>
<th>Solution for nebulizer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone</td>
<td>50-400 (MDI-DPI)</td>
<td>0.2-0.4</td>
</tr>
<tr>
<td>Budesonide</td>
<td>100, 200, 400 (DPI)</td>
<td>0.2, 0.25, 0.5</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>50, 100 (MDI-DPI)</td>
<td></td>
</tr>
</tbody>
</table>


Standard Treatment Options: Bronchodilator + Anti-Inflammatory

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Dose (Microgram)</th>
<th>Duration of action (Hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmeterol/fluticasone</td>
<td>100/50, 250/50, 500/50</td>
<td>12</td>
</tr>
<tr>
<td>Formoterol/budesonide</td>
<td>160/4.5, 804.5</td>
<td>12</td>
</tr>
<tr>
<td>Formoterol/mometasone</td>
<td>200/4.5, 100/4.5</td>
<td>12</td>
</tr>
</tbody>
</table>


Standard Treatment Options: Antibiotics

- Shall be given to patients with:
  - Increased dyspnea, volume and purulence of sputum
  - Increased purulence and other cardinal symptom
  - Mechanical ventilation


Are B2-Agonists Effective and Safe?

Long-Acting B2-Agonists

- Study review of long-acting beta2-agonists for poorly reversible chronic obstructive pulmonary disease:
  - 23 studies (6061 participants)
  - 51 ml change on baseline FEV1 when compared to placebo (95% CI 32-70)
  - Short acting bronchodilator usage reduced 1 puff/day
  - Improvement on St. George’s Respiratory Questionnaire (SGRQ)
  - No difference in exercise tolerance
  - Reduced exacerbations compared to placebo (Number to treat to prevent exacerbation =24)

Safety of LABAs

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Study Year</th>
<th>Study Description</th>
<th>Drugs</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCTs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donahue et al, 2018</td>
<td>Double-blind, flick vs. (n = 269)</td>
<td>salmeterol + fluticasone</td>
<td>No increased incidence of cardiovascular adverse events vs. placebo</td>
<td></td>
</tr>
<tr>
<td>Hill et al, 2008</td>
<td>Single-blind, comparison (n &gt; 500)</td>
<td>fluticasone</td>
<td>No increased incidence of cardiovascular adverse events vs. placebo</td>
<td></td>
</tr>
<tr>
<td>Browne et al, 2005</td>
<td>Double-blind, comparison (n &gt; 200)</td>
<td>formoterol</td>
<td>No serious adverse events reported</td>
<td></td>
</tr>
<tr>
<td>Colombe et al, 2007</td>
<td>Double-blind, comparison (n &gt; 500)</td>
<td>salmeterol + fluticasone</td>
<td>No increased incidence of mortality by comparison vs. salmeterol + fluticasone, placebo</td>
<td></td>
</tr>
<tr>
<td>Campbell et al, 2007</td>
<td>Double-blind, flick vs. (n = 264)</td>
<td>tiotropium</td>
<td>No increased incidence of adverse cardiovascular events vs. placebo</td>
<td></td>
</tr>
</tbody>
</table>

Recent β2-Agonists

- Indacaterol
  - Studies identified on database search (n=70)
  - Excluded: Duplicate studies, abstracts, reviews, pooled analysis. Non-non randomized, non-placebo controlled, retrospective, post-hoc. Acute effects, placebo as the only comparator, asthma patients, inappropriate protocol or outcomes
  - 5 eligible articles: Indacaterol vs. tiotropium (n=2), indacaterol vs. TD-LABA (3)

- Indacaterol vs. tiotropium
  - No difference on trough FEV1 (P=0.27)
  - Less use of rescue inhalers (-0.57 puffs/d, P <.0001)
  - Improvement on TDI score >1 point (63% indacaterol vs. 53% tiotropium, P<0.001)
  - Improvement on SGRQ score with indacaterol (-2.02 units, P<0.0008)
  - No difference in exacerbations, withdrawals, AE, all cause mortality (0.06% vs. 0.32%)

Indacaterol (cont’d.)

- Indacaterol vs. TD LABA
  - FEV1 70 ml higher for indacaterol than TD-LABA (P<0.0001)
  - Reduction in use of rescue inhaler (-0.22 puffs/d, P=0.3)
  - Improvement on dyspnea for indacaterol ( TDI score >1. 63% indacaterol vs. 53% TD-LABA, P .008)
  - Improvement on SGRQ (53% vs. 48%, P=.06)
  - No differences on exacerbations, withdrawals, AE, all cause mortality (0.22% vs. 0.30%)
  - Acute cough within 5 minutes for indacaterol (18% vs. 0.9%)

Muscarinic Antagonists: Effective and Safe?

Tiotropium

- Tiotropium reduced the odds of a COPD exacerbation (OR 0.74; 95% CI 0.66 to 0.83) and related hospitalizations (OR 0.64; 95% CI 0.51 to 0.82) compared to placebo or ipratropium
- Number of patients needed to treat with tiotropium for one year were 14 (95% CI 11 to 22) to prevent one exacerbation and 30 (95% CI 22 to 61) to prevent one hospitalization compared to placebo and ipratropium
- Reductions in these endpoints compared to long-acting β2-agonists were not statistically significant
- Increases in FEV1 and FVC from baseline were significantly larger with tiotropium than with placebo, ipratropium and long-acting β2-agonists over 6 to 12 months
- Dry mouth

Safety of LAMAs

- Anthonisen et al, 2002
  - Lung Health Study: 5 yRCT (n=1,895) tiotropium + smoking intervention
  - Placebo + smoking intervention
  - Increased incidence of death and hospitalization for cardiovascular disease and coronary artery disease vs. placebo (approached statistical significance)

- Casaburi et al, 2002
  - Two identical, double-blind, 1-y RCTs (n = 921) tiotropium, placebo
  - Similar incidence of serious adverse events and death

- Tashkin et al, 2008
  - UPLIFT double-blind, 4-y RCT (n = 5,993) tiotropium, placebo
  - No increased incidence of death or hospitalization for cardiovascular disease and respiratory failure
Safety of LAMAs (cont’d.)

Observational studies, systematic reviews, and meta-analyses

| Lee et al, 2008 Case-control study (n = 32,130 cases and 320,501 control subjects) Various COPD medications Increased risk of all-cause and cardiovascular mortality |
| Ogale et al, 2010 Meta-analysis of 11 RCTs (n = 7,156) Ipratropium Increased risk of cardiovascular events |
| Cala et al, 2008 Meta-analysis of 26 studies, including UPLIFT data (n = 96,790) Ipratropium Increased risk of cardiovascular mortality, myocardial infarction or stroke (composite end point) |
| Kang et al, 2008 Meta-analysis of 19 placebo-controlled RCTs (n = 7,819) Tiotropium No increased risk of all-cause, respiratory and cardiovascular mortality |
| Celli et al, 2010 Meta-analysis of 30 double-blind, placebo-controlled RCTs (n = 19,545) Tiotropium Reduced risk of all-cause mortality, cardiovascular mortality, and cardiovascular events vs. placebo |

Singh et al, 2011 Systematic review and meta-analysis of five RCTs (n = 6,522) Tiotropium Increased risk of mortality with ipratropium bromide and albuterol sulfate inhaler |

Verhamme et al, Two nested case-control studies (n = 6,788) Tiotropium No increased cardiovascular risk or mortality with tiotropium handihaler

Aclidinium Bromide 2014 CHEST Abstract

- CV safety profiles for ACL 400µg BID, from three phase 3, long-term safety studies
- Results:
  - MACE composite scores of serious events were low (DB, n=6, 1.4%; OL, n=7, 1.6%)
  - MACE composite score for all events for the DB & OL studies combined was n=18 (2.0%)
  - Few cardiac AEs were observed

Preferred Usage of Long-Acting Bronchodilators (Anti-cholinergics)

- Tiotropium
  - 24 hour daily anticholinergic
- Aclidinium bromide
  - 12 hour/twice daily anticholinergic

Cardiovascular Safety of Inhaled Long-Acting Bronchodilators

- Of 191,005 eligible patients, 53,532 (28.0%) had a hospitalization or an emergency department visit for a cardiovascular event
- Newly prescribed long-acting inhaled β-agonists and anticholinergics were associated with a higher risk of an event compared with nonuse of those medications (respective adjusted odds ratios, 1.31 [95% CI, 1.12-1.52; P < .001] and 1.14 [1.01-1.28; P = .03])
- Among older individuals with COPD, new use of long-acting β-agonists and anticholinergics is associated with similar increased risks of cardiovascular events

Investigational Treatments and Regimens
indacaterol/glycopyrronium (QVA149) SHINE Study

- SHINE is part of IGNITE Phase III clinical trial program
- Safety and efficacy of dual bronchodilation
  indacaterol/glycopyrronium vs. mono-components indacaterol and glycopyrronium (n= 2144)
- The primary endpoint was trough FEV1 at week 26 for QVA149 versus its mono-components
- Secondary endpoints included dyspnea, health status, rescue medication use and safety

Investigational agent; not FDA approved.

SHINE Study (cont’d.)

- The primary endpoint was trough FEV1 at week 26 for indacaterol/glycopyrronium versus its mono-components
- Secondary endpoints included dyspnea, health status, rescue medication use and safety
- Trough FEV1 at week 26 was significantly improved (p<0.001) with indacaterol/glycopyrronium compared with indacaterol and glycopyrronium (least squares mean [LSM] differences: 0.07 L and 0.09 L, respectively), tiotropium and placebo

Novel LAMA (GSK233705)

- Dose-ranging, parallel-group, double-blind study compared the bronchodilator efficacy, safety and pharmacokinetics of novel LAMA with placebo in patients with moderate-to-severe COPD
- Patients (n=576) were randomized to receive 12.5 µg, 25 µg, 50 µg, 100 µg or 200 µg of novel LAMA or placebo once daily for 28 days
- The primary endpoint was change from baseline in trough forced expiratory volume in 1 s (FEV1) on day 29

Results:
- Novel LAMA produced statistically significant improvements in pulmonary function vs. placebo
- Each dose of novel LAMA was well tolerated and AEs were minimal and similar across all treatment groups
- There were no clinically significant effects on laboratory parameters, vital signs or electrocardiograms

Investigational agent; not FDA approved.

glycopyrronium bromide (NVA237) GLOW3 Trial

- In this multicenter trial, patients were randomized within a cross-over design into two treatment arms: once-daily glycopyrronium bromide 50 µg followed by placebo or placebo followed by once-daily glycopyrronium bromide 50 µg for 3 weeks, with a 14-day washout

GLOW3 Trial (cont’d.)

- Mean trough FEV1 on both days 1 and 21 was significantly higher in patients receiving glycopyrronium bromide (P < 0.05)
- Peak FEV1 on days 1 and 21 was also superior for glycopyrronium bromide
- Patients receiving glycopyrronium bromide showed significantly improved FRC, RV, sGAW, and TLC values versus the placebo on day 21 (P < 0.05)

FRC = Functional residual capacity
RV = Residual volume
TLC = Total lung capacity

Investigational agent; not FDA approved.

M(3)-Selective Muscarinic Antagonist (AZD9164)

- Efficacy in COPD patients (n=28) inhaled single doses of selective muscarinic M(3) antagonist (100, 400 and 1200 µg), tiotropium (18 µg) and placebo at 5 study center visits
- Increase in lung function w/all doses of selective muscarinic M(3) antagonist vs. placebo
- Effect of selective muscarinic M(3) antagonist 400 mg and 1200 mg at 24 h was superior to that seen with tiotropium 18 mg

Investigational agent; not FDA approved.
Case Study No. 2

- 63-year-old female
- 40 packs/year history of smoking (still smoking)
- 5-7 years of progressive decrease on exercise tolerance
- DOE affecting daily activities for the past two years, since first hospitalization for pneumonia
- Stays at home, no longer traveling
- Co-existing hypertension
- Medications:
  - Losartan HCT
  - Ipratropium/albuterol PRN
  - Aspirin

Case Study No. 2 (cont’d.)

Physical exam:
- Normal V.S. O2 sat on room air at rest 92%
- No jugular venous distension (JVD)
- Prolonged expiratory phase of the ventilation
- Distant heart sounds
- Trace lower extremity edema

Case Study No. 2 (cont’d.)

- Chest x-ray with hyperinflation changes
- Echocardiogram with right ventricular systolic pressure (RVSP) 35 mm Hg
- 6MWT: 305 meter, O2 sat on R.A. declined to 85%

New/Investigational Treatments

- Lung volume reduction surgery
  - Patient selection, cost, mortality, specialized centers.
- Bronchoscopic lung volume reduction
  - Endobronchial placement of one way valves
  - Plugs and blockers
  - Endobronchial instillation of sealants
  - Thermal airway ablation
  - Airway stents for decompression of bullae


Future Directions in the Management of COPD

- Simplification of treatment
  - Combination of long acting bronchodilators
  - Combination of Super long acting bronchodilators
  - Combination LABA +LAMA +ICS
- Novel anti-inflammatory agents
- Smoking cessation. Are e-cigarettes safe?
- Phenotype based therapy
- Stem cell therapy
- Reduction of mortality

Summary

- Modern treatment of COPD must include:
  - Smoking cessation
  - Long acting bronchodilators are preferred for patients with FEV1 < 80%
  - LABA and LAMA are safe an effective medications
  - Combination just make sense
  - Trial of ICS
  - Address hypoxemia, malnutrition, inflammation and comorbidities
  - Rehabilitation and vaccines
  - New therapies in the horizon