New Medications in the Treatment of COPD

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Objectives

- Review pathophysiology of COPD
- Review new methods of inhaled medication delivery
- Identify newly (or soon to be) available therapeutic agents for the treatment of COPD and their place in the therapeutic armamentarium
COPD

- Chronic Obstructive Pulmonary Disease (COPD) is a common preventable and treatable disease.
- 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.
Healthcare Costs

- $49.9 Billion Total Annual Costs
- $29.5 Billion Direct Costs
  - ~16.3 Million Office Visits
  - ~1.5 Million ED Visits
- $20.4 Billion Indirect Costs
  - Lost work time
  - Patient and Family Members
Healthcare Costs

• Direct Costs

• Between 50 and 75% Due to Exacerbations

• $7,200 / routine admission

• $21,000 / severe admission

• $45,000 / ICU admission mechanical ventilation
COPD

3rd leading cause of death in the US\textsuperscript{1}

Only leading cause of death which increased from 2007 – 2011
COPD Risk Factors

• Complex Gene / Environment Interaction
  • Familial Risk of airflow obstruction in NonSmoking Siblings of Patients with COPD

• Alpha-1-antiprotease deficiency

• Other (genome-wide association studies)
  • Less Clear Association
    • Matrix Metalloproteinase 12
    • Hedge-hog interacting protein
    • Alpha-nicotinic acetylcholine receptor
COPD Risk Factors

- Tobacco Smoking
  - Cigarettes
  - Cigar / Pipe
- Environmental Smoke ("second hand")
- Home / Workplace
- Other "Leafy" Substances
COPD Risk Factors

- Air Pollution
- Urban Environment
- Socioeconomic Status
- Smoking Prevalence
- Other Factors
  - Not well defined
  - Environmental air
  - Crowding
  - Poor nutrition
  - Recurrent Infections
COPD Pathophysiology

• Chronic Airflow Obstruction
  • Obstructive Bronchiolitis (Small airways disease)
  • Parenchymal Destruction
    • Loss of alveolar tethering
  • Bronchomotor Tone

• Chronic Airway Inflammation
  • Structural Changes
    • Small Airway Narrowing
Treatment

• Goals
  • Reduce COPD symptoms
  • Decrease frequency and severity of exacerbations
  • Improve health status and exercise tolerance
  • Reduce Mortality
    • Oxygen

• Oxygen
Treatment

• Goals
  • Reduce Disease Progression
    • No treatment shown to decrease the inexorable decline in pulmonary function
    • Reduction in exacerbations may reduce progression by decreasing lung injury
Treatment

- Nonpharmacologic
  - Smoking Cessation
  - Nutritional Support
  - Patient Education
- Mechanical Devices
  - Improve secretion clearance
  - Acapella
  - Flutter
Treatment

• Nonpharmacologic
  • Pulmonary Rehabilitation
    • No improvement in lung function
    • Improvement in exercise tolerance / VO2_{max}
    • Improved Quality of Life
    • Decreased Hospitalization
  • Vaccination
Vaccination

- Influenza (AIV)
  - Annual trivalent / tetravalent

- Pneumococcal polysaccharide (PPSV23)
  - 6 – 10 years

- Pneumococcal conjugate (PCV13)
  - New recommendations CDC (Sept 2014)
  - ≥ 65 y/o 1 dose
  - Separated from AIV and PPSV23
Pharmacologic Options

• Inhaled
  • Beta$_2$ Agonists
    Short Acting  Long Acting
  • Anticholinergics (AntiMuscarinics)
    Short Acting  Long Acting
• Corticosteroids
• Combination Products
Pharmacologic Options

• Systemic
  • Methylxanthenes
  • Theophylline
  • Caffeine
  • Oxygen
  • Phosphodiesterase 4 Inhibitors
3’,5’ cAMP

- Secondary intracellular messenger
- Regulates post-translational modification (phosphorylation) of multiple intracellular enzymes
- Adenylyl cyclase
- Cyclic Nucleotide Phosphodiesterases (1 – 11)
  - cGMP selective (5, 6, 9)
  - cAMP selective (4, 7, 8)
  - Nonselective (1, 2, 3, 10, 11)
3’,5’ cAMP

- Hydrolyzes 3’,5’ cAMP to 5’AMP
- Increased intracellular cAMP levels
  - Goblet cell hyperplasia
  - Increased eosinophil (neutrophil) infiltration/activation
- Lung Inflammation / Injury
- Airway Remodeling
Phosphodiesterase 4 (PDE 4)

• Inhibition
  • Decreased eosinophil infiltration, lung injury, airway wall thickness, goblet cell hyperplasia
  • Decreased secretions
PDE 4 Inhibitors

- Rofumilast
  - Reduced PMNs (31%) Eosinophils (42%)
  - 17% reduction in moderate to severe exacerbations
- Number Needed to Treat: 4.35
Delivery Devices

• Metered Dose Inhalers
• Dry Powder Inhalers
• Soft Mist Inhalers
• Aerosol Nebulizers
Metered Dose Inhalers

• CFC (Freon 12)
• Discontinued
  • Beginning 2008
  Albuterol
  • Last 31 Dec 2013
  Combivent (albuterol/ipratropium)
  Maxair (pirbuterol)
Metered Dose Inhalers

- HFA (HydroFlouroAlkane)
- r134a
- Qualitatively different from CFC inhalers
  - Warmer
  - More viscous
  - Less forceful
  - Cannot use “float” technique
Dry Powder Inhalers

• Manufacturer Specific
• Capsule
• Self-Contained
Capsule Inhalers

- Neohaler
- Arcapta (indacaterol)
- Seebri (glycopyrronium)
- Aerolizer
- Foradil (formoterol)
Capsule Inhalers

- HandiHaler
- Spiriva (tiotropium)
Self Contained Inhalers

- Twisthaler
- Asmanex (mometasone)
- Flexhaler
- Pulmicort (budesonide)
Self Contained Inhalers

- Preshaler
- Tudorza (aclidinium)
- Discus
- Advair (fluticasone/salmeterol)
- Serevent (salmeterol)
- Flovent (fluticasone)
Self Contained Inhalers

- Ellipta
- Breo (fluticasone/vilanterol)
- Anoro (vilanterol/umeclidinium)
- Incruse (umeclidinium)
- Arnuity (fluticasone furoate)
Soft Mist Inhalers

- Respimat
- CombiVent (albuterol/ipratropium)
- Spiriva (tiotropium)
- Striverdi (olodaterol)
- olodaterol/tiotropium
Pharmacologic Options

- Inhaled
  - Beta$_2$ Agonists
    - Short Acting
    - Long Acting
  - Anticholinergics (AntiMuscarinics)
    - Short Acting
    - Long Acting
  - Corticosteroids
  - Combination Products
Short Acting Beta Agonists (SABA)

• Historical
  • Epinephrine (Primatene Mist)
  • Isoproterenol (Isuprel)
  • Isoetharene (Bronkometer)
  • Metaproterenol (Alupent)

• Current
  • Albuterol (Ventolin, Proventil, ProAir)
  • Levalbuterol (Xopenex)
Short Acting Anticholinergics (SAMA)

- Ipratropium
  Atrovent HFA (2004)
Long Acting Beta Agonists (LABA)

- Black Box Warning (Asthma)
- No similar warning for COPD
Long Acting Beta Agonists (LABA)

- Salmeterol (1994) (Serevent)
- Formoterol (2001) (Foradil)
Long Acting Beta Agonists (LABA)

- **Indacaterol (2011)**
  - (Arcapta)
  - 75 mcg dosage
  - European approval 150 and 300 mcg

- **Vilanterol (2013 as combination therapy)**
  - (not marketed independently)

- **Olodaterol (2014)**
  - (Striverdi)
Long Acting Anticholinergics (LAMA)

- Aclidinium (2012) (Tudorza)
Long Acting Anticholinergics (LAMA)

• Tiotropium (2004) (Spiriva)
• Umeclidinium (2014) (Incruse)
• Glycopyrronium/NVA237 (pending) (Seebri)
Inhaled Corticosteroids (ICS)

- Fluticasone Propionate (Flovent)
  Furoate (Arnuity)
- Mometasone (Asmanex)
- Budesonide (Pulmicort)
Combinations

• LABA / ICS
  • Advair (2000/2003)
    (Fluticasone Propionate / Salmeterol)
  • Symbicort (2006/2009)
    (Budesonide / Formoterol)
  • Dulera (2010)
    (Mometasone / Formoterol)
Combinations

- LABA/ICS
  - Breo (Fluticasone furoate / Vilanterol)
  - Boehringer Ingelheim (unknown / Olodaterol)
Combinations

- LABA/LAMA
- Anoro (Vilanterol/Umeclidinium)
Combinations

- LABA/LAMA
  - Actavis (Formoterol/Aclidinium)
    - FDA submission pending
  - Boehringer Ingelheim (Tiotropium/Olodaterol)
    - Phase 3 trials
  - Ultibro/Xoterna/QVA149 (Indacaterol/Glycopyrronium)
    - European approval
    - US Phase 3 trials
Combinations

- LABA / LAMA / ICS
  - GlaxoSmithKline
  - Vilanterol / Umeclidinium / Fluticasone Furoate
  - Phase 3 Trials
GOLD Guidelines

• Originally 2001
• Treatment recommendations based on severity of airflow obstruction
GOLD Guidelines

• Major Revision 2011
• Updated 2013, 2014
• Treatment based on a combined assessment of symptoms/risk of exacerbations and airflow obstruction
Combined Assessment

- Assess symptoms
- Assess risk of exacerbations
- Assess degree of airflow limitation using spirometry

Combine these assessments for the purpose of improving management of COPD
Symptoms

- COPD Assessment Test (CAT)
- Clinical COPD Questionnaire (CCQ)
- Modified British Medical Research Council Questionnaire (mMRC)
Risk of Exacerbation

- High Risk
  - $\geq 2$ exacerbations / year
  - or $\geq 1$ hospitalization / year
  - or $\text{FEV1} \leq 50\%$ predicted
Airflow Obstruction

• FEV1/FVC ratio ≤ 0.70
• Mild (GOLD 1) FEV1 > 80% predicted
• Moderate (GOLD 2) 50% ≤ FEV1 < 80%
• Severe (GOLD 3) 30% ≤ FEV1 < 50%
• Very Severe (GOLD 4) FEV1 < 30%
Combined Assessment

Risk (Exacerbation history)

(C) Risk ≥ 2 or ≥ 1 (leading to hospital admission)

(D) Risk > 1 (not leading to hospital admission)

Symptoms

Risk (GOLD Classification of Airflow Limitation)

(A) Risk 0 (CAT < 10 mMRC 0–1)

(B) Risk 1 (CAT ≥ 10 mMRC ≥ 2)

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Treatment Recommendations

• Goals
• Decrease symptoms
• Decrease exacerbations
• Improve exercise tolerance
• Improve health status
Treatment Recommendations

- Risk Based
- Severity of Disease
- GOLD Grouping
- Combined Assessment
All Patients
(GOLD A – D)

• Smoking Cessation
• Patient Education
• Nutritional Support
• Vaccination

• Pulmonary Rehabilitation
  Symptomatic / Increased risk
  (GOLD B – D)
Pharmacologic

• All Patients
• Short Acting Bronchodilators
  • prn use
    • SABA (albuterol or levalbuterol)
    • SAMA (ipratropium)
    • SABA+SAMA (Combivent)
GOLD A
Less Symptomatic / Minimal Airflow Obstruction / Low Risk of Exacerbations

• prn bronchodilators
  • SABA or SAMA
  • SABA+SAMA
GOLD B

More Symptomatic / Limited Airflow Obstruction / Low Risk of Exacerbations

• Nature of Symptoms
  • Dyspnea / Exertional Dyspnea
  • Sputum Production
GOLD B

More Symptomatic / Limited Airflow Obstruction / Low Risk of Exacerbations

• Dyspnea
• LABA
• LAMA
• Persistent Symptoms
• LABA+LAMA
GOLD B
More Symptomatic / Limited Airflow Obstruction / Low Risk of Exacerbations

• Sputum Production
  • LABA / ICS
  • LAMA / ICS
• Exacerbations
  • GOLD C
GOLD C

Less Symptomatic / Severe Airflow Obstruction / Higher Risk of Exacerbation

• LABA / ICS
• LAMA
• Exacerbations
  • Add PDE4 Inhibitor
GOLD D

More Symptomatic / Severe Airflow Obstruction / High Risk of Exacerbation

- LABA / ICS
- LAMA
- LABA / LAMA / ICS
- LAMA / ICS
- Exacerbations
- Add PDE4 Inhibitor
Not Recommended

- Antioxidants
- Oral Mucolytics
  - guaifenesin, iodinated glycerol, etc.
- N-acetylcysteine
- Inhaled corticosteroids (monotherapy)
- Systemic corticosteroids (chronic)
- Theophylline
Summary

• Multiple new therapeutic options for the treatment of COPD
• 1 new class of agents: PDE4-Inhibitors
• New variations on a theme
Summary

- Long acting bronchodilators
- More convenient and effective for symptom relief
- Daily dosing: improved compliance
Summary

• Combination Therapy
• Improved compliance
• Reduced cost
• Improved efficacy
• Reduced side effects
• Compared to increased dose of single agent
Summary

• Single Daily Dosing

• LABA
  • Indacaterol
  • Vilanterol
  • Olodaterol

• LAMA
  • Aclidinium (BID)
  • Umeclidinium
  • Glycopyrronium
Summary

• Single Daily Dosing

• LABA/LAMA
  • Vilanterol/Umeclidinium (Anoro)
  • Olodaterol/Tiotropium
  • Indacaterol/Glycopyrronium

• LABA/ICS
  • Vilanterol/Fluticasone furoate (Breo)
  • unknown/Olodaterol
Summary

- Phosphodiesterase 4 Inhibitors
  - Rofumilast (Daliresp)
Summary

• Exciting time in Pulmonary Medicine
• Many new and upcoming agents
  • Improve compliance
  • Improve symptoms
  • Reduce costs
    Patients and Insurance co.