Current Landscape of COPD Treatment

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GOLD: Global Initiative for Chronic Obstructive Lung Disease

**GOLD definition of COPD**

- Common, preventable, treatable—partially reversible
- Characterized by persistent airflow limitation
- Usually progressive and disabling
- Associated with enhanced chronic inflammatory response in airways/lung to noxious particles or gases

**COPD is heterogeneous**

- Multiple risk factors, phenotypes, comorbidities
- Exacerbations and comorbidities contribute to severity

The Impact of COPD in the United States

- COPD prevalence in U.S.
  - estimates range from 5.1% to 6.2%
  - Gender: Adult women > men (6.1% vs. 4.1)

- In 2010, COPD accounted for
  - 10.3 million physician office visits/y
  - 1.5 million ED visits
  - 699,000 hospital discharges

- Costly
  - Direct COPD (2010): $29.5 billion/y
  - Indirect (2010): $20.4 billion/y

- Third leading cause of death

- Fourth leading cause of hospital readmissions

COPD: The Old Look

Perception\textsuperscript{3,4,5}

COPD is a disease of the elderly\textsuperscript{1}
COPD is a disease of men\textsuperscript{2}

COPD in Younger Patients and Women Is on the Rise

Reality

Reality: COPD afflicts the working-age population.
Reality: COPD is also a disease of women.

COPD: The New Look

Environmental level
- Diet
- Pollution
- Infections
- Temperature
- Smoking
- Allergens
- Activity

Clinical level
- Cancer
- COPD
- Metab Syn.
- Osteoporosis
- Myopathy
- CVD

Biological level
- Innate immunity
- Acquired immunity
- Repair
- Oxidative stress
- Ageing
- Bioenergetics
- GWAS
- Epigenetics
- miDNA
- miRNA
- ncRNA
- Pharmacogenomics

Genetic level
- Genetic markers
- Diagnostic biomarkers
- Therapeutic targets
- Integrated care
- Personalized medicine
- Guidelines network
- Life-style
  - Modifiable factors

Agusti A, Vestbo J. AJRCCM 2011;184: 507 - 513
Risk Factors for COPD

**Smoking**¹,²
(~80% of cases)
- Current or former smoker

**Genetic factors**¹,²
- Alpha-1 antitrypsin deficiency
  (~2-3% of emphysema cases in US)
  - Can cause COPD even without smoking history/environmental exposure

**Environmental exposure**² (10% - 20% of cases)
- Long-term exposure to chemicals, dust, or fumes in the workplace; second-hand smoke
- Household exposures (eg, biomass cooking)

**Age**²
- >40 years of age

Pathophysiology of COPD

Environmental and occupational exposure

Genetic susceptibility

Childhood respiratory infections

Alveolar macrophage (IL-8, GRO-α, LTB4)

CD8+ T lymphocyte

MCP-1

Protease inhibitors

(α-AI, TIMPs)

Airway inflammation and remodeling

Proteases

Neutrophil

Tissue destruction

Airflow Limitation

Barnes PJ. Chest. 2000;117(suppl):10S-14S.
Inflammatory and Cellular Mechanisms in COPD due to Cigarette Smoking

Emphysema and Small Airways Disease Contribute to Total Airflow Limitation in COPD


**Normal**

Airway held open by alveolar attachments (elastin fibers)

**COPD**

- Disrupted alveolar attachments (emphysema)
- Mucosal inflammation, fibrosis
- Mucus hypersecretion and inflammatory exudate

Airway obstructed by:
- Loss of alveolar attachments
- Mucosal inflammation and fibrosis
- Luminal obstruction with inflammatory exudate and mucus

Hyperinflation, central to the pathophysiology of COPD (i.e., increased airway resistance), correlates more directly with patient-reported outcomes.
Improving Outcomes in COPD

- Early diagnosis and accurate assessment

COPD Is Underdiagnosed and Undertreated

1. NIH, NHLBI. Morbidity and Mortality: 2009 Chart Book on Cardiovascular, Lung and Blood Diseases.
Key Indicators for COPD Diagnosis

- Consider a diagnosis of COPD, and perform spirometry, if any of these indicators* are present in an individual >40 years of age
  - Exertional dyspnea
  - Chronic cough
  - Chronic sputum production
  - History of exposure to risk factors (eg, tobacco smoke)
- Spirometry is required to make the diagnosis
  - Post-bronchodilator FEV₁/FVC <0.70 confirms persistent airflow limitation and COPD diagnosis

*These indicators are not diagnostic in themselves, but the presence of multiple key indicators increases the probability of a COPD diagnosis. FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity.

Diagnostic Challenges: Natural History of COPD

Significant drops in lung function often required for patients to become severely symptomatic.
Diagnostic Challenges: COPD Phenotypes

Disease attributes that describe the diverse symptoms and outcomes of patients

- Frequent Exacerbations
- Exercise/Activity Intolerance/ Hyperinflation
- Chronic Cough and Sputum
- Radiologic Airway (CB, bronchiectasis), Emphysema
- Asthma COPD Overlap Syndrome (ACOS)
- Chronic Hypoxemia
- Chronic Respiratory Failure`
- Comorbidities Cardiac, Nutritional
- Symptom Burden

Patient-Related Diagnostic Challenges

- Patients lack of awareness of the disease
- Patients under-report symptoms
- Symptoms are chronic and slowly progressive, often misattributed to aging
- SOB leads to activity reduction to reduce symptom impact (thus, need to assess level of activity which requires time-consuming focused questions)
- Availability of healthcare resources/insurance issues
- Social stigma of COPD

Clinician-Related Diagnostic Challenges

• Myths about COPD
• Nihilistic attitude about COPD/Awareness of COPD guidelines suboptimal
• Diagnosis of exclusion and overlap with other diseases
• Underuse and paucity of validated assessment tools
• Inadequate utilization of spirometry

Global Strategy for Diagnosis, Management, and Prevention of COPD: Assessment of COPD

1. Assess symptoms

2. Assess degree of airflow limitation using spirometry

3. Assess risk of exacerbations
# GOLD: Combined COPD Assessment

**Assessment Using Symptoms, Breathlessness, Spirometric Classification, and Risk of Exacerbations**

<table>
<thead>
<tr>
<th>Risk (GOLD Classification of Airflow Limitation)</th>
<th>CAT &lt; 10</th>
<th>CAT ≥ 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Symptoms</td>
<td>Symptoms</td>
</tr>
<tr>
<td>3</td>
<td>mMRC 0-1</td>
<td>mMRC ≥2</td>
</tr>
<tr>
<td>2</td>
<td></td>
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</tr>
<tr>
<td>1</td>
<td></td>
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</tr>
</tbody>
</table>

- **A** Low risk, Less symptoms
- **B** Low risk, More symptoms
- **C** High risk, Less symptoms
- **D** High risk, More symptoms

- **Risk (Exacerbations/Year)**
  - ≥2 or ≥1 leading to hospital admission
  - 1 (not leading to hospital admission)
  - 0

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When assessing risk, choose the highest risk according to GOLD grade or exacerbation history.
Global Strategy for the Diagnosis, Management, and Prevention of COPD: Assessment of COPD

1. Assess symptoms

2. Assess degree of airflow limitation using spirometry

3. Assess risk of exacerbations

4. Assess comorbidities
These comorbid conditions may influence mortality and hospitalizations; the patient should be assessed for them routinely and treated appropriately.
Improving Outcomes in COPD

- Early diagnosis and accurate assessment\(^1\)
- Implementing optimal management\(^2\)

Goals of Management

- Airflow Limitation
  - Improve Lung Function
    - Slow FEV$_1$ Decline
- Symptom Burden
  - Improve Symptoms
- Exacerbations
  - Prevent and Manage Exacerbations
- Functional Limitations
  - Improve Health Status and Exercise Tolerance

Reduce Hospital Admissions and Mortality
Nonpharmacologic Therapy To Manage COPD

- Smoking Cessation
- Patient Education
- Oxygen Therapy
- Pulmonary Rehabilitation
- Vaccination
- Surgical and Non-surgical Alternatives

Nonpharmacological Options for COPD

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk, fewer symptoms</td>
<td>Low risk, more symptoms</td>
<td>High risk, fewer symptoms</td>
<td>High risk, more symptoms</td>
<td></td>
</tr>
</tbody>
</table>

**Description**

- **GOLD 1-2**: < 1 Exacerbation, mMRC 0-1 or CAT ≤ 10
- **GOLD 1-2**: < 1 Exacerbation, mMRC > 2 or CAT > 10
- **GOLD 3-4**: > 2 Exacerbations, mMRC 0-1 or CAT ≤ 10
- **GOLD 3-4**: > 2 Exacerbations, mMRC > 2 or CAT > 10

**Essential**

- Smoking cessation for all patients who smoke
  - The key intervention for smokers
  - Can include pharmacologic treatment

**Recommended**

- Pulmonary rehabilitation
- Physical activity
- Influenza vaccination
- Pneumococcal vaccination

Adapted from Global Initiative for Chronic Obstructive Lung Disease; (GOLD) 2014. www.goldcopd.org.
Smoking Cessation

- **Ask** about tobacco use
- **Advise** to quit
- **Assess** willingness to make an attempt
  - Motivational intervention
- **Assist** in quit attempt
- ** Arrange** follow-up

- Smoking status and willingness to quit assessed at every health visit
- Individual readiness to quit is variable
  - May be related to acute health care events
- Exploit windows of opportunity
  - Acute health problems are associated with increasing cessation rates
Pharmacologic Therapy: First Line

- NRT, bupropion and varenicline are superior to placebo
- Bupropion and NRT show equal efficacy when compared head to head
  - Bupropion has not been shown to enhance the effect of NRT compared with NRT alone
- Varenicline is superior to bupropion and single forms of NRT
  - Varenicline is not more effective than combination NRT

Pharmacologic: Alternative Therapy

- Second line (off label use) but have documented efficacy and are recommended as alternative therapies
  - Nortriptyline
    - Nortriptyline did not enhance the effect of NRT compared with NRT alone
  - Clonidine
    - Clonidine increased the chances of quitting, but this was offset by a dose-dependent rise in adverse events

- Nonpharmacologic options
  - Acupuncture (effects due to positive expectations)
  - Hypnosis (no common technique to analyze)

E-Cigarettes

• Rationale behind E-cigarettes
  – Cigarette smoke contains up to 7000 chemicals
  – Nicotine is not among the most important toxic compounds
  – Nicotine replacement using a preparation that does not contain the health-compromising toxins

• Harm reduction - supporting an addiction
  – Nicotine delivery is unregulated
  – Contain flavorants and other additives whose effects are unknown
  – Concern many smokers who would have quit switch to E-cigarettes
  – Some persons may start e-cigarettes because of perceived safety
    • After becoming addicted may be at higher risk to switch to conventional cigarettes

Defining Pulmonary Rehabilitation: Official ATS/ERS Statement

“Pulmonary rehabilitation is a comprehensive intervention based on a thorough patient assessment followed by patient tailored therapies that include, but are not limited to, exercise training, education, and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviors.”

ATS = American Thoracic Society; ERS = European Respiratory Society

Components of Pulmonary Rehabilitation Programs

- **Exercise Training**
  Involves the measurement of a number of physiologic variables, including maximum oxygen consumption, maximum heart rate, and maximum work performed.

- **Nutrition Counseling**
  Positive effects have been observed when nutritional supplementation is proposed alone or as an adjunct to exercise training.

- **Education Including Smoking Cessation**
  Most important topics include smoking cessation, info on COPD, therapy, self-management skills, etc. Specific contributions of education to the improvements seen after pulmonary rehabilitation remain unclear.

- **Assessment and Follow-up**

Pharmacological Management of COPD

• Guideline-recommended COPD treatment
  - Improves lung function
  - Minimizes symptoms
  - Improves QoL
  - Prevents exacerbations

• Wide variety of options including new agents
  - Appropriate treatment selection hinges on GOLD staging
  - Before stepping up/modifying treatment, re-evaluate

  Treatment goals
  Clinical phenotype
  Comorbidities
  Adherence
Rationale for Early Treatment in COPD

- The effect of treatment on lung function may be more marked in patients who are younger and in those with less severe disease\textsuperscript{1-4}

- Lung function deteriorates more rapidly during the less severe, early stages of COPD\textsuperscript{3}

- LABA and LAMA are recommended initial maintenance therapy for patients who are symptomatic but at low risk of exacerbations\textsuperscript{5}

- Lack of data in treatment-naïve patients with mild or moderate airflow limitation\textsuperscript{1}

COPD Pharmacological Agents Approved

**Bronchodilators**

**Short-acting**
- β-Agonists (SABA)
  - Albuterol
  - Pirbuterol
  - Levalbuterol
- Anticholinergic (SAMA)
  - Ipratropium

**Long-acting**
- β-Agonists (LABA)
  - Salmeterol
  - Formoterol
  - Arformoterol
  - Indacaterol
  - Olodaterol
- Anticholinergic (LAMA)
  - Tiotropium
  - Aclidinium
  - Umeclidinium
- LABA + LAMA
  - Umeclidinium + Vilanterol
  - Tiotropium + Olodaterol
- Theophylline

**Anti-Inflammatory**

**ICS+LABA**
- Fluticasone + Salmeterol
- Budesonide + Formoterol
- Fluticasone Furoate + Vilanterol

**PDE-4 Inhibitors**
- Roflumilast

**Systemic Steroids**
- Prednisone
- Methylprednisolone
# COPD Pharmacological Treatment Options

Adapted from: Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease 2011.

<table>
<thead>
<tr>
<th>First Choice</th>
<th>Second Choice</th>
<th>Alternative Choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-acting (SAMA OR SABA)</td>
<td>Long-acting (LAMA OR LABA)</td>
<td>Theophylline</td>
</tr>
<tr>
<td></td>
<td>Long-acting (LAMA + LABA)</td>
<td>Short-acting (SAMA + SABA)</td>
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</table>

- **LAMA**
- **ICS + LABA**
- **Combinations of:**
  - LAMA
  - LABA
  - ICS
  - PDE4 Inhibitor*

Adapted from: Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease 2011.
Many Patients Remain Symptomatic on “Mono-Bronchodilator” Therapy

- A significant proportion of patients with COPD remain symptomatic when receiving a single bronchodilator\(^1\)

**Current guidelines recommend adding a second bronchodilator to treatment regimens in moderate COPD to optimize symptom benefit for patients\(^2\)**

- Combining bronchodilators of different pharmacologic classes may improve efficacy and decrease the risk of side effects compared to increasing the dose of a single bronchodilator\(^2\)

- As airflow obstruction becomes more severe, a LAMA plus a LABA combination has been advocated\(^3\)

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Improving Outcomes in COPD

• Early diagnosis and accurate assessment

• Implementing optimal management

• Incorporating self-management skills through education and collaboration with a healthcare team

Patient Education: Key Educational Messages for COPD

- Basic facts about COPD
  - Contrast normal and COPD airways
- Roles of medications and potential adverse events
  - Long-term maintenance and quick-relief medications
- Relevant environmental triggers and reducing exposures
- Building an action plan: when and how to take rescue actions
- Skills
  - Inhalers, nebulizers, spacers, symptoms, and early warning signs
Adherence to COPD Medications Is Poor

- More than half of patients with COPD will stop new prescriptions after the first month\(^1\)
- Sustained adherence continues to decay over time\(^1\)
- Strategies to support adherence
  - Educate patients about COPD and treatments\(^2\)
  - Set treatment goals\(^2\)
  - Urge patients to complete treatment course\(^2\)
  - Train patients on proper use of devices periodically\(^2\)
  - Support self-efficacy; encourage and praise success\(^3\)
  - Ask about side effects\(^2\)
  - Ask about device preference\(^4\)

Inhaler Devices Available in the U.S.

A large proportion (49-76%) of patients use their inhalers incorrectly. GOLD guidelines recommend rechecking inhaler technique at each patient visit.

Nebulization Has a Role for Many Patients and in Multiple Settings

**Settings**
- At home
- Long-term care
- Hospital inpatient
- Emergency room
- Unable to use MDI/DPI devices appropriately
- Inadequately controlled on current therapy
- Those who prefer nebulization
- Cognitively impaired
- Physically impaired
- Very Young and Very Old

Unmet Needs With Current Interventions

- Current pharmacotherapies do not change the natural history of COPD\(^1\)
- Many patients remain symptomatic with current therapies\(^2\)
- Inadequate adherence with inhaled therapy is a major cause of poor clinical outcomes in the treatment of COPD\(^3\)
- Cost, compliance, and safety are significant issues\(^3\)

Emerging Therapies in COPD Management

- Novel therapies
  - Novel formulations of existing medications
  - Novel classes of bronchodilators
  - Novel targets for pharmacologic therapy
Novel Formulations of Existing Medications

- Novel Bronchodilators
  - Ultra LABAs
  - Ultra LAMAs
  - LABA/LAMA combinations
  - LABA/ICS combinations
  - Nebulized bronchodilators and combination therapies
  - MABAs

LABA: long acting beta-2 agonists; LAMA: long acting muscarinic antagonist; ICS: inhaled corticosteroid; MABA: bifunctional muscarinic beta-2 agonist

Drugs Used in Treatment of Comorbidities That May Be Useful in COPD

- Statins
- ACE Inhibitors
- Beta-blockers
- Peroxisome proliferator-activated receptor (PPAR) agonists
- Macrolides
Chemotactic factors
IL-8, CXC Chemokines

Other irritants (LPS)
Alveolar macrophage

Oxidants

LTB4

Alveolar macrophage

Mediator antagonists:
LTB4 (5-LO inhibitor)
Chemokine (IL-8), TNF inhibitors; CXCR2 antagonists

Proteases

Neutrophil elastase
Cathepsins
MMPs
IL-6, IL-17

NAC (BRONCUS)

Fibroblast

CD8 + lymphocyte

DCs

TGFβ
CTG
II-6

Fibrosis

Emphysema

Mucous hypersecretion

Antifibrotics:
TGF-β inhibitor

Muco-regulators:
EGFR, CACC inhibitors

Neutrophil elastase
Cathepsins
MMPs
IL-6, IL-17

Protease inhibitors:
NE, MMP, cathepsin

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**Bronchoscopic Approaches to LVR**

**Flow regulation**
- **Zephyr-Endobronchial Valves (EBV)**
  - PulmonX
  - One-way valve leads to atelectasis.

**Tissue compression**
- **Intrabronchial Valves (IBV)**
  - Spiration
  - One-way valve leads to atelectasis.

  **RePneu - Lung volume reduction coil (LVRC)**
  - PneumRx
  - Coil reduces lung volume by coiling and compressing disease tissue.

  **AeriSeal - Polymeric Lung Sealant**
  - Aeris
  - Tissue sealant flows into alveolar compartment, polymerizes and seals target area.

  **InterVapor - Bronchoscopic Thermal Vapor Ablation (BTVA)**
  - Uptake
  - Heated water vapor produces thermal reaction with localized inflammation followed by fibrosis.
Summary (1) Improving Outcomes in COPD

- Early diagnosis and accurate assessment
  - Identifying patients at risk
  - Using appropriate diagnostic approaches, ruling out other mimickers
  - Early treatment
- Implementing optimal management
  - Reducing exposures to risk factors and triggers
  - Non-pharmacological approaches
  - Pharmacological treatments
- Incorporating self-management skills through education and collaboration with a health care team
  - Improve adherence

• Proper assessment of COPD should include assessment of symptoms, lung function, and exacerbation risk to determine appropriate treatment\textsuperscript{1}

• Comorbidities are common and adversely affect outcomes\textsuperscript{1}

• Phenotypic characterization of COPD will improve personalized approach to the disease\textsuperscript{2}

• Smoking cessation, pulmonary rehabilitation can improve outcomes\textsuperscript{1}

• Current and emerging therapeutic combinations may be more effective than monotherapy\textsuperscript{1}

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