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COPD 2009

Chronic obstructive pulmonary disease (COPD) has a natural history marked by:

- Lung function that persistently declines due to airflow obstruction, expressed in terms of FEV₁;
- Airflow obstruction and lung function limitation that is not fully reversible;
- Persistent symptoms that increase in severity with advancing disease and age of the patient;
- Exacerbations that become more frequent in association with lung function impairment; and,
- Mortality risk that increases with the frequency and severity of exacerbations, and may have both respiratory and non-respiratory components.

COPD progression cannot be reversed by any therapeutic measures known today. Progression may be slowed, however, and frequency of exacerbations reduced by therapeutic intervention in a majority of patients who have not reached the most severe stage of disease. Thus, although COPD is a relentlessly progressive disease, it should not be regarded as an untreatable disease.

An initial step in effective treatment is recognition and correct diagnosis of COPD as the cause of a patient's symptoms. COPD is often untreated or incorrectly treated because it is unrecognized and/or misdiagnosed—for example, identifying airflow limitation as an indication of asthma rather than of COPD. Also contributing to under-recognition of COPD is failure to recognize the small but significant number of patients whose decline in lung function is due to alpha₁ antitrypsin deficiency. Failure to recognize the underlying pathophysiology can result in progressive decline of lung function due to a condition that can be effectively treated.

Clinical trials and evidence from clinical practice have shown over the past two decades that the progressive natural history of COPD can be altered by therapeutic intervention. The frequency and severity of exacerbations can both be reduced by pharmacologic intervention using long-acting bronchodilators, inhaled corticosteroids, or drugs in various combinations. A combination of two or three drugs has been shown to reduce exacerbations more effectively than single drugs.¹

Reduction of frequency and severity of exacerbations lowers risk for mortality but also improves overall health status and quality of life for the patient. Pharmacologic intervention alone cannot be depended

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upon to achieve improvement regarding exacerbations. Patient self-management can be equally important—for example, compliance with a therapeutic regimen, avoidance of triggering factors such as tobacco smoke, and recognition of early signs and symptoms of impending exacerbation.

Smoking cessation is an important element—for many patients, perhaps the most important element—of self-management. Smoking cessation can, at all stages of COPD severity, contribute to slowing of FEV₁ decline, symptom improvement, and decrease in exacerbation frequency and severity.

While bronchodilation therapy alone has been shown to modify symptoms, it has no demonstrable effect on progressive FEV₁ decline. The rate of FEV₁ decline may be reduced by inhaled corticosteroids (ICS) or by combination therapy using ICS and long-acting beta agonist (LABA). Effective pharmacotherapy that slows FEV₁ decline may also lower risk for mortality.² Interventions influencing risk for mortality include smoking cessation, supplemental oxygen for hypoxic patients, and ICS/LABA or anticholinergic therapy.

Effective pharmacologic management of COPD must be based on recognition of COPD as a disease of multiple pathogenic factors:

- Mucociliary dysfunction;
- Structural changes in lung tissues;
- Airway inflammation; and,
- Systemic inflammation and extra-pulmonary complications.

Although multidimensional, COPD is a treatable disease for which goals of effective management can be established:

- Relieve symptoms—e.g., dyspnea, fatigue, depression;
- Improve exercise tolerance;
- Improve overall health status;
- Prevent and treat complications—e.g., pneumonia, cardiovascular problems;
- Help patients become competent in self-management;
- Prevent exacerbations;

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- Treat exacerbations promptly and effectively when they occur;
- Prevent or slow disease progression, recognizing that airway structural changes and lung function decline cannot be reversed; and,
- Reduce risk for mortality.

Treatment goals should be assessed by reliable outcome measures for the interventions.

The value of smoking cessation in treatment of COPD is a message that merits frequent repetition and emphasis. Current pharmacologic smoking cessation therapies are applied orally, by transdermal patch, or by inhalation. All have demonstrated benefit in clinical trials. Smoking status should be a subject for discussion at every patient visit, and smoking cessation offered to currently smoking patients. Smoking history can have important bearing on determining a patient's risk for COPD and its complications.

Recommendations for COPD therapy at each stage of disease are delineated in guidelines published by the Global Initiative for Chronic Obstructive Lung Disease (GOLD), accessed at

<http://www.goldcopd.com>. The GOLD guidelines indicate that pharmacotherapy should be introduced at the earliest stage of COPD whenever possible, when the disease is mild and stable. All patients are regarded as qualifying for a trial of pharmacotherapy, although changes in lung function after a brief course of bronchodilator therapy can be small and not predictive of other clinically related outcomes.³ In the overall management of stable COPD, bronchodilators are a mainstay of symptom management. The rational use of bronchodilators in COPD is based upon their physiologic effects and associated symptom improvement.⁴

The recently reported Understanding the Potential Long-Term Impact on Function with Tiotropium (UPLIFT) Trial added information about use of this anticholinergic in COPD therapy. Significant and sustained increases in lung function were demonstrated by tiotropium versus control over the 4-year study period.⁵ Tiotropium may be regarded as a first-line therapy for patients with persistent symptoms.

Long-term studies of ICS/LABA in COPD included:

- Towards a Revolution in COPD Health (TORCH) Trial,⁶ and
- Investigating New Standards for Prophylaxis in Reducing Exacerbations (INSPIRE) Trial.⁷

Both trials added information that broadens the scope of pharmacotherapy for COPD.

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Potential adverse effects of COPD pharmacotherapy include:

- Bronchodilators—possibility of cardiovascular effects,
- ICS—oral candidiasis and dysphoria, pneumonia, loss of bone density.

Suspected or diagnosed infection in a COPD patient may indicate the need for an antibiotic.

Identification of a specific organism can be difficult by either sputum analysis or blood culture. Antibiotic choice should generally be made empirically to cover *H. influenzae*, *S. pneumoniae* and *M. catarrhalis*.

A summary of effective approach to pharmacologic therapy for COPD includes:

- Currently available medications can reduce symptoms, improve health status and reduce frequency and severity of exacerbations;
- Long-acting bronchodilators should be considered as front-line therapy for all patients with symptomatic COPD;
- Addition of ICS to pharmacotherapy should be considered with severely decreased FEV₁ and patients with recurrent exacerbations; and,
- ICS/LABA combination therapy is shown to be superior to either agent used alone in improving FEV₁ and reducing frequency and severity of exacerbations.

Despite improvements in COPD definition and approaches to therapy, COPD is still frequently treated more as an acute than as a chronic disease. This results in inadequate disease control.⁸ The fault may lie less with individual physicians or patients, more with a faulty model for delivery of medical care and health services.

Delivery of medical care frequently follows an acute-care model:

- Orientation to acute illness, focused on acute symptoms and laboratory test results;
- Patient-physician interactions are kept as brief as possible and are often unproductive;
- Treatment goals stress short-term relief of symptoms; and,
- No role is identified for patient self-management.

In contrast, a chronic-care model for COPD followed in several studies:

- Is focused on health promotion and patient self-management, and

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- Has long-term goals for prevention of complications and exacerbations, improved quality of life, and reduced health-care utilization.⁹

A chronic-care model for COPD is also more likely to recognize comorbidities:

- Physical—extra-pulmonary disease, pulmonary and extra-pulmonary complications, pulmonary infections, lung cancer, osteoporosis, muscle wasting, GERD/peptic ulcer,¹⁰⁻¹²
- Psychological—depression, anxiety or both.¹³⁻¹⁵

The pathogenic role of inflammation in COPD has gained increased attention and understanding. Airway inflammation is central to the initiation and progression of COPD. Tobacco smoking initiates the processes of inflammation, making it a major contributor to initiation of the pathogenic processes of COPD. Advancing age is also associated with decline in lung function, and other factors may be involved as well.¹⁶

It is also now understood that inflammation is not confined to the lungs in COPD. Inflammation in the lungs “spills over” into systemic circulation and affects other tissues and organs. Pathologic cardiovascular effects and systemic muscle weakness are among the “spill-over” clinical effects of COPD inflammation. Others can include reduced functional capacity and health status, impaired bone metabolism, normocytic anemia, cancer, diabetes, and peptic ulcer.¹⁷

A definition of “chronic systemic inflammatory syndrome” has been suggested for functional abnormalities that develop in patients >40 years old with a smoking history of >10 pack-years.

Recognizing the broader systemic effects of inflammation in COPD provides an opportunity to identify novel targets for pharmacotherapy. This approach is contrary to current COPD treatment with bronchodilators and corticosteroids that targets airway symptoms and attempts to minimize systemic effects. Anti-inflammatory agents that have potential for addressing systemic aspects of COPD include:¹⁸

- Selective phosphodiesterase inhibitors;
- Glycoaminoglycans;
- Antioxidants;

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- Statins;
- Angiotensin-converting enzyme (ACE) inhibitors;
- Angiotensin II type 1 receptor antagonists; and,
- Peroxisome proliferator-activated receptor (PPAR) agonists.

Of drugs in current use, ICS is effective in reducing systemic inflammation as assessed by C-reactive protein (CRP) serum level. The known association of increased CRP level and cardiovascular disease suggests that more aggressive use of ICS might reduce cardiovascular complications of COPD.¹⁹ The ICS/LABA combination has been shown to be associated with reduction of all-cause mortality compared with use of ICS alone and placebo.⁶

Phosphodiesterase 4 (PDE 4) inhibitors are approved for treatment of other diseases, and are under investigation for treatment of COPD and its systemic inflammatory complications. The selective PDE 4 inhibitor roflumilast has been shown to cause a dose-dependent inhibition of tumor necrosis factor-alpha (TNF-alpha).²⁰

Oxidative stress, especially as it is associated with tobacco smoke, has been of interest as a target for COPD therapy. A review of epidemiologic studies indicated that antioxidant administration (vitamin c and E, beta-carotene) has some effect in decreasing the incidence and severity of COPD.²¹ In a study of another approach to COPD treatment, a large placebo-controlled trial with the mucolytic N-acetylcysteine did not show any significant effect in reducing incidence of COPD exacerbations.²²

Statin drugs, prescribed primarily to patients with cardiovascular risk factors, are of growing interest for effects of airway and systemic inflammation. Potential effects of statins are proposed for T cells, macrophages, bronchial epithelial cells, and smooth muscle cells. Studies have found statin use to be associated with attenuated decline in lung function in elderly patients and patients who are smokers or former smokers.^{23,24} Defective apoptotic cell clearance in asthma and COPD has been proposed as a new target for statins.²⁵

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The complex expression and effects of PPARs in airway structural cells and skeletal muscle has been of interest in developing drugs that influence PPAR pathways. Under current investigation also are approaches to neutralize inflammatory mediators such as TNF-alpha and Interleukin-8.

References

1. Van Noord JA, de Munck DR, Bantji TA, et al. Long-term treatment of chronic obstructive pulmonary disease with salmeterol and the additive effect of ipratropium. *Eur Respir J* 2000; 15:878-885.
2. Soriano JB, Vestbo J, Pride NB, et al. Survival in COPD patients after use of salmeterol and/or fluticasone propionate in general practice. *Eur Respir J* 2002; 20:819-825.
3. Celli BR, MacNee W. Standards for the diagnosis and treatment of COPD. *Eur Respir J* 2004; 23:932-946.
4. Hanania NA, Donohue JF. Pharmacologic interventions in chronic obstructive pulmonary disease: bronchodilators. *Proc Am Thorac Soc* 2007; 4:526-534.
5. Tashkin DP, Celli B, Senn S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008; 359:1543-1554.
6. Calverly PMA, Anderson JA, Celli B, TORCH Investigators, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007; 356:775-789.
7. Wedzicha JA, Calverley PM, Seemungal TA, et al. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. *Am J Respir Crit Care Med* 2008; 177:19-26.
8. <http://www.improvingchroniccare.org>
9. Adams SG, Smith PK, Allan PF, et al. Systematic review of the chronic care model in chronic obstructive pulmonary disease prevention and management. *Arch Intern Med* 2007; 167:551-561.
10. Mannino DM, Watt G, Hole D, et al. The natural history of chronic obstructive pulmonary disease. *Eur Respir J* 2006; 27:627-643.

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11. Holguin F, Folch E, Redd SC, et al. Comorbidity and mortality in COPD-related hospitalizations in the United States, 1979 to 2001. *Chest* 2005; 128:2005-2011.
12. Di Marco F, Verga M, Reggente M, et al. Anxiety and depression in COPD patients: The roles of gender and disease severity. *Respir Med* 2006; 100:1767-1774.
13. Kunik ME, Roundy K, Veazey C, et al. Surprisingly high prevalence of anxiety and depression in chronic breathing disorders. *Chest* 2005; 127:1205-1211.
14. Van Ede L, Yzermans CJ, Brouwer HL. Prevalence of depression in patients with chronic obstructive pulmonary disease. *Thorax* 1999; 54:688-692.
15. Yohannes AM, Baldwin RC, Connolly MJ. Depression and anxiety in elderly patients with chronic obstructive pulmonary disease. *Age Ageing* 2006; 35:457-459.
16. Buist AS, Burnie MA, Vollmar WM, et al. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. *Lancet* 2007; 370:741-750.
17. Cazzola M, Matera MG, Rogliani P, et al. Treating systemic effects of COPD, *Trends Pharmacol Sci* 2007; 28:544-550.
18. Fabbri LM, Rabe KF. From COPD to chronic systemic inflammatory syndrome? *Lancet* 2007; 370:797-799.
19. Sin DD, Man SF, Marciniak DD, et al. The effects of fluticasone with or without salmeterol on systemic biomarkers of inflammation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2008; 177:1207-1214.
20. McCluskie K, Klein U, Linnevers C, et al. Phosphodiesterase type 4 inhibitors cause proinflammatory effects in vivo. *J Pharmacol Exp Ther* 2006; 319:468-476.
21. Tabak C, Smit HA, Rasanen L, et al. Dietary factors and pulmonary function: a cross-sectional study in middle aged men from three European countries. *Thorax* 1999; 54:1021-1026.
22. Decramer M, Rutten-van Molken M, Dekhuijzen PN, et al. Effects of N-acetylcysteine on outcomes in chronic obstructive pulmonary disease (Bronchitis Randomized on NAC Cost-Utility Study, BRONCUS): a randomized placebo-controlled trial. *Lancet* 2005; 365:1552-1560.
23. Alexeeff SE, Litonjua AA, Sparrow D, et al. Statin use reduced decline in lung function. VA Normative Aging Study *Am J Respir Crit Care Med* 2007; 176:742-747.
24. Keddissi JI, Younis WG, Chbeir EA, et al. The use of statins and lung function in current and former smokers. *Chest* 2007; 132:1764-1771.

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25. Walsh GM. Defective apoptotic cell clearance in asthma and COPD—a new drug target for statins? *Trends Pharmacol Sci* 2008; 29:6-11.

Standard of Practice

Chronic obstructive pulmonary disease (COPD) is under-recognized and frequently under-treated or erroneously treated. Under-recognition is often a result of treating the patient for acute symptoms and not recognizing the chronic nature of the disease. COPD also may be misdiagnosed as asthma.

Suspicion for COPD should be raised by the smoking history of any patient who presents with respiratory symptoms. Questions about current and/or former tobacco smoking should be included in every patient interview.

Tobacco smoke, especially cigarette smoke, is a major pathogenic factor in COPD. The oxidative stress of inhaled tobacco smoke is known to initiate the inflammatory processes that damage airways and may enter systemic circulation to cause extra-pulmonary complications of COPD. Treatment of COPD should include smoking cessation at all stages of disease from early/mild to severe/unstable. Smoking cessation is beneficial at all stages of COPD.

A salient feature of the natural history of COPD is persistent decline in lung function (FEV_1). No currently known therapy can fully reverse decline in FEV_1 . Effective therapeutic intervention can, however, usually slow FEV_1 decline if the disease is correctly diagnosed and understood as a chronic disease.

Symptom management is the therapeutic goal in early, mild, stable COPD, and long-acting bronchodilators are first-line therapy at this stage. Long-acting bronchodilators do not slow FEV_1 decline but are effective in managing early respiratory symptoms. As airflow obstruction increases with advancing airway inflammation, slowing of FEV_1 decline becomes a principal therapeutic goal. Inhaled corticosteroids (ICS) may be added singly, or in a LABA/ICS combination. With increase in COPD severity, the likelihood of exacerbation increases. Increased frequency and severity of exacerbations increased

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risk for mortality. Reducing frequency and severity of exacerbations is a principle goal of therapy in more severe stages of disease.

While FEV₁ decline is attributable to airway inflammation and progressive airway obstruction, advancing age is also an important contributing factor to decline in lung function.