Therapeutic options for chronic obstructive pulmonary disease: present and future

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Abstract. – By 2020, chronic obstructive pulmonary disease (COPD) will become the third leading cause of mortality and fifth leading cause of disability worldwide. Although traditionally therapeutic nihilism has dominated the approach to the management of COPD patients, it is becoming increasingly clear that COPD is a highly preventable and treatable condition. Smoking cessation is the most important therapy because it is the only intervention that has been shown to modify the accelerated decline in lung function that is characteristic of COPD. Domiciliary oxygen therapy for those who are hypoxemic at rest results in improved survival. Vaccinations and immunizations against influenza and pneumococcus should be encouraged. Bronchodilators are used for symptomatic relief. Recent introduction of long-acting bronchodilators facilitates good control of dyspnea with once or twice daily dosing. In conjunction with inhaled corticosteroids, they appear to produce added clinical benefits. Pulmonary rehabilitation and lung transplantation are other therapeutic options for select groups of patients. Many promising compounds are in various stages of development as future therapies in COPD. Drugs such as phosphodiesterase 4 inhibitors, tyrosine kinase blockers and peroxisome proliferator-activated gamma receptor agonists show great promise as disease-modifying agents in COPD.

Key words: COPD, Management, Pharmacotherapeutics, Review, Tutorial.

Introduction

Chronic obstructive pulmonary disease (COPD) is a major global health problem, affecting 5 to 10% of the adult population and responsible for 3 million deaths worldwide annually1,2. In the United States (US) alone, COPD accounts for 6% of all deaths3. In 1993, the costs of COPD morbidity and mortality in the US were estimated to be $23.9 billion. Direct treatments for COPD-related illness accounted for $14.7 billion, and the remaining $9.2 billion were related to indirect costs resulting from COPD morbidity and mortality4. What is more discouraging is that the public health impact of COPD will grow rapidly over the next twenty years. Experts predict that COPD, which in 1990 was ranked as the sixth leading cause of mortality worldwide, will rise to become the third leading cause by 2020 and will account for more than 6 million deaths annually5. Furthermore, COPD will become the fifth most common cause of disability in the world (currently 12th leading cause of disability)5. While these figures are alarming, they most certainly underestimate the true health burdens of COPD, as airflow obstruction is an important contributor to other common causes of morbidity and mortality, including ischemic heart disease, stroke, pneumonia and lung cancer6-10.

Although traditionally therapeutic nihilism has dominated COPD management, there is a growing recognition that COPD is a very preventable and treatable condition1. This, in part, reflects a better understanding of the cellular and molecular mechanisms of COPD and the development of novel therapies that can improve health outcomes (such as quality of life and exacerbations) of COPD patients. In this paper, we will provide an overview of the current and future therapies for COPD.

COPD is defined as a state “characterized by airflow limitation that is not fully reversible. The airflow limitation in most cases is both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases”11. This progressive and relentless loss of lung function is the result of emphysema due to destruction of lung
parenchyma and narrowing of small airways likely arising from chronic inflammation and airway remodeling. A hyperresponsiveness is also a common feature of COPD, affecting 60 to 80% of COPD patients and is more common in women than in men. In over 80% of the cases, cigarette smoking is causally linked to the development of COPD. Other risk factors include exposure to biomass, noxious gases, ambient pollution, and chronic respiratory infections. A diagnosis of COPD should, therefore, be considered in current or former smokers (or in never smokers with other risk factors), who present with cough, sputum production, or dyspnea, and with spirometric evidence of irreversible airflow obstruction in the absence of asthma or bronchiectasis.

### Smoking cessation strategies

Smoking cessation is the single most important therapy for improving health outcomes in COPD patients. Indeed, smoking cessation is the only therapeutic intervention so far shown to modify the accelerated rate of decline in FEV₁, which is one of the hallmarks of COPD. Whereas the rate of FEV₁ decline in sustained smokers is on average ~60 ml/year, it is only ~30 ml/year in ex-smokers. Importantly, smoking cessation reduces all-cause mortality rates by ~27% (95% confidence interval [CI] 1% to 47%), driven largely by very significant reductions in cardiovascular mortality (relative risk [RR] compared to continued smokers, 0.54; 95% CI, 0.32 to 0.92). Despite massive public health campaigns, taxation policies, and legislations to discourage cigarette consumption, 20 to 25% of the adult population continue to smoke. Moreover, even among those who want to stop smoking, sustained quit rates remain suboptimal. One reason for this is that nicotine is highly addictive. A single physician recommendation for smoking cessation is associated with a very modest ~5% long-term abstinence rate. Despite this low success rate, given the importance of smoking cessation on the long-term health status of COPD patients, health professionals should use every opportunity to advocate smoking cessation in such patients. Smoking cessation rates can be vastly improved when advice from health professionals can be coupled with other interventional modalities. A detailed discussion of smoking cessation programs and methods are beyond the scope of this article. Excellent articles on this topic have been published by the US Department of Health and Human Services and other similar organizations. Briefly, these organizations recommend an integrated program of behavioral and pharmacological support to aid in smoking cessation over many weeks to months. With multi-disciplinary approach to smoking cessation consisting of cessation counseling, education, and nicotine replacement therapy (or treatment with antidepressants such as bupropion and nortriptyline), the long-term abstinence rates can be as high as 25% in patients in early COPD. One-time interventions are rarely effectual. Relapses are common and usually occur during periods of emotional, psychological or physical stress. It may be accompanied by use of psychotropic medications or alcohol. Thus, clinicians should closely follow their patients for any early signs of relapse. For those who do relapse, counseling, education and nicotine replacement therapy should be offered.

### Bronchodilators

Unfortunately, even in the “best” programs, less than a third of smokers become “sustained” quitters. Furthermore, although smoking cessation improves the natural history of COPD, once COPD becomes clinically apparent, many sustained quitters remain symptomatic and their airways persistently inflamed. Thus, in symptomatic patients with COPD, additional therapies are usually indicated. One of the cardinal features of COPD are narrowed airways arising from multiple causes including excess vagal tone, decreased lung elastic recoil pressure, and airway remodeling from chronic inflammation. Bronchodilators, which open up airways, are therefore commonly used to reverse airflow limitation and
to improve symptoms in COPD. In general, bronchodilators fall into two large categories: anticholinergics and β₂-agonists.

**Anticholinergics**

Anticholinergic agents antagonize the action of acetylcholine on M3 muscarinic receptors, thereby attenuating smooth muscle tone in the airways that depends largely on cholinergic stimulation. Ipratropium is a short-acting anticholinergic agent that is commonly used in aerosolized form to induce bronchodilation in COPD. Ipratropium works within 10 to 20 minutes of inhalation, reaching its peak action at 30 minutes to an hour. Its bronchodilatory effect dissipates gradually over 2 to 3 hours. Tiotropium is a longer-acting anticholinergic agent. Like ipratropium, tiotropium has a quaternary ammonium structure and has equal affinity for M1, M2, and M3 receptors in the human airways. However, relative to ipratropium, tiotropium dissociates very slowly from the M1 and M3 receptors but more rapidly from the M2 receptors. This property makes tiotropium approximately 10-times more potent and longer-acting than ipratropium. The half-life of tiotropium is greater than 36 hours and its bronchodilatory effect increases with daily dosing reaching its peak after 1 week of continued therapy. This allows once-a-day dosing in most circumstances. Clinical trials of tiotropium have uniformly demonstrated a beneficial effect in reducing exacerbation rates compared to placebo by about 25%. Tiotropium also improves health-related quality of life in COPD relative to placebo. However, there are no convincing data to date that they are superior (or inferior) to long-acting β₂-agonists in reducing exacerbation rates or improving health status in patients with moderate-to-severe COPD. Moreover, the current trials were too short and underpowered to evaluate the effects of these drugs on all-cause mortality. Long-acting anticholinergics have a powerful effect on FEV₁. In the two trials that had one year follow up, FEV₁ increased by 121 ml compared to placebo or ipratropium monotherapy. In the two trials that compared long-acting anticholinergics to LABAs, over a 6 month period, long-acting anticholinergics had a more favorable effect on FEV₁ (+37 ml). Because quaternary amines are less well absorbed than most other anticholinergic agents, tiotropium has fewer systemic side effects than non-specific anticholinergics such as atropine. The most common side effect is dry mouth, which may reflect direct deposition of the drug in the oropharynx during inhalation or may arise from systemic absorption of the drug in the lungs. Urinary retention has also been reported, but less frequently than dry mouth. Tiotropium should therefore be used cautiously in elderly men with COPD. Although systemic absorption is less with tiotropium than with other anticholinergic agents, some systemic absorption does occur. Whether the amount of systemic absorption is large enough to affect cardiovascular autonomic tone is unknown.

Although the long-term cardiovascular effects of tiotropium have not been fully elucidated, there are some disconcerting data on ipratropium. Ipratropium bromide may increase the risk of cardiovascular complications in COPD by 10 to 20%. In the Lung Health Study (LHS), for instance, those assigned to ipratropium had a 3.7 fold increase in the risk of arrhythmias than those assigned to placebo. The LHS investigators also found that those assigned to ipratropium bromide had a 26% increase in the risk of cardiovascular events, compared with the group assigned to placebo. The risk of fatal cardiovascular events was even higher (relative risk, 2.6). The risk of non-fatal cardiovascular events was only modestly elevated (relative risk, 1.19). Although this study was underpowered to detect cardiovascular events, these data, nonetheless, raised concerns that ipratropium bromide may increase cardiovascular morbidity and mortality in COPD. In another study, Kaya and co-workers found that, in the time domain analyses of electrocardiographic data, ipratropium administration resulted in a significant reduction in the mean R to R interval, the mean SDNN and the mean RMSSD during handgrip exercise compared with baseline values (775 ± 30 ms vs. 748 ± 21 ms, P <0.05; 57 ± 5 ms vs. 50 ± 5 ms, P <0.05; 30 ± 2 ms vs. 26 ± 2 ms, P <0.01, respectively). These data suggest that ipratropium can modulate autonomic tone during mild exertion, which may make susceptible myocardium more vulnerable to arrhythmias and other serious cardiac events.
The other class of bronchodilators commonly used in COPD is the β₂-agonist. Traditionally, inhaled short-acting β₂-agonists have been used either on an as-needed basis for “rescue care” or on a regular basis to prevent or reduce symptoms. Although these medications produce only a modest improvement in lung function in COPD, studies have demonstrated that they reduce symptoms, improve exercise tolerance and decrease the frequency of exacerbations. However, there is no evidence that these medications have any effect on the rate of decline in lung function or survival.

β₂-agonists bind to specific cell surface receptors, which are members of the transmembrane, G-protein coupled receptor family. Following ligand binding to the active site of the receptor, the β-component of the associated Gs-protein dissociates and activates adenylate cyclase, leading to the production of intracellular cyclic adenosine monophosphate (cAMP), and subsequent activation of protein kinase A (PKA). PKA then phosphorylates a number of intracellular regulatory proteins and cAMP induces relaxation of bronchial smooth muscles.

β₂-agonists can be divided into 2 categories based on their duration of action: short and long-acting β₂-agonists. In general, short acting β₂-agonists have a rapid onset of action (within 5 minutes of inhalation) reaching peak action at 1 to 2 hours. Their effect wears off by 3 to 4 hours. The bronchodilatory action of long-acting β₂-agonists (LABA), on the other hand, lasts for more than 12 hours, making them suitable for twice daily formulations. Currently, there are two agents available for use in this class: salmeterol and formoterol. Salmeterol is a partial agonist with an onset of action slower than that of the short-acting β₂-agonists. Formoterol is a complete agonist and has an onset of action similar to that of short-acting β₂-agonists. The mechanisms of action of the LABAs, salmeterol and formoterol have been reported previously. Briefly, salmeterol partitions into the cell membrane and diffuses laterally to the β₂-adrenoceptor. The side chain of the molecule then binds to a discrete, hydrophobic region of the fourth transmembrane domain, the exo-site. Formoterol, which is moderately lipophilic, is taken up into the cell membrane as a depot. The drug then progressively leaches out to activate the β₂-receptor, imparting a prolonged, concentration-dependent action. Along with their bronchodilatory effects, some have suggested that LABAs may have anti-inflammatory properties, particularly when combined with corticosteroids. However, there are not enough data from clinical experiments to validate this notion.

Placebo-controlled clinical trials in COPD have demonstrated that LABAs produce a ~21% reduction in COPD exacerbation rates compared with placebo. They also improve health related quality of life of COPD patients (St. George’s Respiratory Questionnaire, SGRQ, 2.8 unit improvement compared to placebo). Predictably, they also increase FEV₁, on average, by 82 ml compared with placebo. However, they do not appear to modify the long-term decline in FEV₁.

The most common side effects of these medications are palpitations and tremor. Hypokalaemia and ventricular arrhythmias can also occur but infrequently. These systemic complications likely arise because these medications are absorbed into the systemic circulation through the pulmonary and gastrointestinal systems. The latter occurs because some drug particles are deposited directly into the oropharynx and later swallowed by patients. Proper use of inhaler devices will reduce the amount of oral deposition and, hence, reduce the total systemic bioavailability of these drugs. The most important potential systemic target of action and of side effects is the heart. Although β₁-receptors predominate, β₂-receptors are also present in the myocardium. Upon stimulation, these receptors mediate increases in both ventricular contractility and sympathetic outflow to the heart. These effects can be blocked with β-receptor antagonists such as atenolol. In asthma, where there are more safety data available on LABAs, there is a growing concern that LABA mono-therapy may be associated with increased morbidity and mortality. Indeed, one post-marketing surveillance study was halted prematurely because of safety concerns over salmeterol. In an interim analysis, the salmeterol group showed a nonsignificant trend toward more asthma-related life-threatening events (in-
these cells interact to produce and propagate COPD is largely unknown.
Many chemokines and cytokines have now been implicated in COPD. Genetic polymorphisms in tumor necrosis factor, interleukin-1β, interleukin-6, α-1-antitrypsin, metalloproteinases (e.g., MMP-9) and certain anti-oxidants have been associated with progression of COPD, suggesting the possible involvement of these molecules in the pathogenesis of COPD. However, the exact pathogenic mechanism(s) remain poorly understood due in part to a scarcity of good animal models of COPD that can mimic the human COPD condition and by the complexity of the human immunologic system. Nevertheless, there is little doubt that inflammation and its byproducts are critically involved in the pathogenesis of COPD and its complications. This new paradigm has resulted in the gradual shift in emphasis in pharmacologic targets from airway smooth muscles to inflammatory cells.

Inhaled corticosteroids

The use of inhaled corticosteroids remains one of the most contentious issues in COPD pharmacotherapy. In placebo-controlled trials, inhaled corticosteroids appeared to reduce COPD exacerbation rate by 24% relative to placebo. It is also clear that patients with moderate to severe COPD experience larger reductions in exacerbations with steroid use than those with milder disease. Inhaled corticosteroids also improved health status of COPD patients relative to placebo (SGRQ, 1.4 unit improvement relative to placebo). Their effects on mortality are unknown. Several epidemiologic studies demonstrated reductions in mortality with inhaled corticosteroids; however, several have shown a null association. There is a clinical study currently underway that should provide a definitive answer to the mortality question. A contentious issue is whether inhaled corticosteroids modify the rate of decline in FEV1. Several meta-analyses have been published to address this question. The totality of evidence indicates that over the first 3 to 6 months of therapy, inhaled corticosteroids should be used cautiously in COPD. A u and colleagues, for example, studied 630 patients with unstable angina or myocardial infarction and 10,486 control subjects enrolled in seven Veterans Administration Medical Centers, and found that compared with subjects who did not fill a short acting β2-agonist, patients who had filled one β2-agonist prescription in the 3-month prior to their index date had ~70% excess risk for an acute coronary event. Importantly, the excess risk was limited to those patients who had a prior history of cardiovascular disease; their risk was over three-fold higher than those who did not use β2-agonists. A diotonally, new users of β2-agonists had a seven-fold increase in the risk of cardiovascular events. Future studies are needed to validate these initial epidemiologic observations and to determine the potential mechanisms by which these medications may increase cardiovascular risk in susceptible COPD patients.

Inflammation in COPD

COPD is characterized by inflammation involving both the airways and the lung parenchyma. The earliest inflammatory lesions are found in the small, peripheral airways, even before patients experience a significant decline in lung function. Inflammation appears to play a central role in the pathogenesis of airway fibrosis, lung proteolysis and mucus hypersecretion, which turn, contributes to bronchitis, bronchiolitis and emphysema. To date, most of the attention has been paid to macrophages and neutrophils. However, other cells such as CD-8 positive lymphocytes, mast cells and epithelial cells are also likely to be involved in the initiation and progression of COPD. How
corticosteroids improve FEV₁ by ~45 mL relative to placebo. After the first 6 months, they improve FEV₁ by 5 to 7 mL per year relative to placebo, indicating only a very modest effect of steroids on the rate of decline in FEV₁. This magnitude of change is not likely to be clinically relevant.

Inhaled corticosteroids are fraught with certain side effects. The incidence of oral thrush is almost three times higher in users of inhaled corticosteroids than in non-users. Users are also more likely to have dysphonia and to experience bruising compared with non-users by two-fold and 1.6 fold, respectively. The effects of inhaled corticosteroids on bone mineral density, osteoporosis, and cataracts are much more controversial. Clinical trials have failed to demonstrate an increased incidence of cataract in COPD patients treated with inhaled corticosteroids (RR 1.05; 95% CI 0.84 to 1.31). The two trials that evaluated the effects of inhaled corticosteroids on bone mineral density (BMD) in COPD showed a net 1.6% reduction in BMD of the femoral neck and 1.1% reduction of the lumbar spine when compared to placebo. There was no excess risk of fractures within a three year follow-up period (RR 0.70). The life-time risk of fractures in those who continue to use inhaled corticosteroids for longer than 3 to 4 years is unknown.

Combined therapy with LABA and inhaled corticosteroids

Some have suggested that combined therapy with LABAs and inhaled corticosteroids may lead to better health outcomes than that with individual component therapy. In vitro studies indicate that corticosteroids can improve the efficiency of coupling between the β₂-receptor and its ligand. This may increase β₂-receptor-stimulated adenylate cyclase activity, leading to superior bronchodilation. Moreover, there are data to indicate corticosteroids may maintain β₂-receptor sensitivity to its ligand even with chronic exposure to β₂-agonists, thereby preventing desensitization and tolerance to chronic β₂-agonist therapy in COPD. LABAs may prime glucocorticoid receptors for binding with corticosteroids and increase the efficiency of translocation of receptor-corticosteroid complex from cell cytosol to nucleus where the primary action of corticosteroids takes place. Despite these theoretical advantages of combination therapy in COPD, there is a paucity of clinical data, which have demonstrated a synergistic effect of combination therapy on airway inflammation in COPD.

There have several high-quality large randomized clinical trials that have compared head-to-head the effects of inhaled corticosteroids, LABA, combination therapy and placebo on exacerbations or lung function. In many studies, combination therapy was superior to placebo and monotherapy with individual components in improving lung function and health-related quality of life and reducing clinically relevant exacerbations. Combination therapy reduced exacerbations by 48% compared with placebo. Combination therapy was better than mono-therapy with LABA by 33% or mono-therapy with inhaled corticosteroids by 26% in reducing exacerbation rates. The clinical studies also indicate that combination therapy is better than mono-therapy with inhaled corticosteroids (SGRQ, mean standardized effect estimate, –0.19; 95% CI, –0.29 to -0.10), LABAs (SGRQ, mean standardized effect estimate, –0.13; 95% CI, –0.23 to –0.03) or placebo (SGRQ, mean standardized effect estimate, –0.26; 95% CI, –0.35 to –0.16) in improving health-related quality of life of COPD patients.

Data from clinical trials indicate that combination therapy is also more effective than placebo, inhaled corticosteroids or LABAs alone in improving FEV₁. The standardized mean difference in FEV₁ between combination therapy and placebo was 0.47 (95% CI, 0.30 to 0.64); between combination therapy and inhaled corticosteroids was 0.34 (95% CI, 0.26 to 0.43); and between combination therapy and LABAs was 0.26 (95% CI, 0.18 to 0.34). These data suggest an additive benefit of inhaled corticosteroids and LABAs on FEV₁.

The treatment effects of combination therapy appear to be more pronounced among those with severe or very severe disease. In the TRISTAN trial, for instance,
participants with FEV\textsubscript{1} less than 50% of predicted showed a significantly greater increase in pre-dose FEV\textsubscript{1} and significantly less rescue medication use at 1 year with combination therapy. Patients with more severe disease experienced a 30% reduction in the rate of exacerbation compared with placebo; whereas, in those with FEV\textsubscript{1} 50% or greater, the relative reduction in exacerbations was only 10%. Further studies are required to investigate whether synergy can be demonstrated in COPD using other clinical endpoints.

Although none of the randomized trials were powered on mortality, combination therapy appears to be safe. In the 3 trials that reported on mortality, there was a trend (though insignificant) towards lower mortality with combination therapy over placebo (RR, 0.66; 95% CI, 0.32 to 1.38)\textsuperscript{98}. The risks of significant side effects (defined as cough, exacerbation of COPD symptoms, headaches, tremor, vertigo, or candidiasis) from combination therapy are similar to those related to placebo in carefully selected patients, who follow proper inhaler techniques\textsuperscript{99}.

Vaccination

Although there is little available evidence for the usefulness of influenza and pneumococcal vaccination for COPD patients per se, they have been demonstrated in the general elderly population to reduce all-cause, pneumonia, and cardiac hospitalizations\textsuperscript{91,92} and deaths\textsuperscript{93} by 30 to 40% with only minor excess risks to recipients. Since most COPD patients are elderly, and are also at increased risk of hospitalizations and mortality from various cardiovascular conditions and pneumonia\textsuperscript{93}, influenza and pneumococcal vaccination should also be instituted for most COPD patients.

Future targets for novel therapy

Given the prominence and likely importance of lung inflammation in the pathogenesis of COPD, pro-inflammatory cells and cytokines are increasingly popular targets for new drug development. A n example of these new targets are the phosphodiesterase-4 (PD4) inhibitors\textsuperscript{94}. PDE4 is a major cyclic adenosine-3',5'-monophosphate-metabolizing enzyme and its inhibitors have been shown to relax bronchial smooth muscles, to reduce airway inflammation, and to modulate the pulmonary nervous system\textsuperscript{94}. Although in general they appear to be better tolerated than the non-specific PDE inhibitors such as theophylline, they may still produce nausea and vomiting in a small proportion of patients. Moreover, their clinical efficacy appears to be much more modest than what would have been predicted based on pre-clinical studies\textsuperscript{95}.

Leukotriene B\textsubscript{4} (LTB\textsubscript{4}) is another therapeutic target. LTB\textsubscript{4} is a potent chemoattractant of neutrophils and is found in relatively large concentrations in induced sputum from COPD patients. There are two subtypes of LTB\textsubscript{4} receptors: BLT1 and BLT2. Antagonists for these receptors are being explored for possible therapeutic effects\textsuperscript{96}. Tumor necrosis factor (TNF) levels are also increased in COPD airways and these molecules may be responsible for activation of metalloproteinases, which may, in turn, mediate matrix breakdown and emphysematous changes in the lung parenchyma of COPD patients\textsuperscript{97}. TNF inhibitors and receptor blockers are under evaluation for possible therapeutic effects in COPD.

Kinases have pleiotrophic effects on the immune system. Certain kinases activate and promote inflammatory activities that may contribute to on-going airway inflammation and remodeling in COPD\textsuperscript{98}. Tyrosine kinase inhibitors are currently used in the treatment of chronic myelogenous leukemia. They are encouraging data from animal studies that similar drugs may have activities in downregulating airway inflammation\textsuperscript{98}. Clinical studies are being planned for the future to evaluate the clinical efficacy of these compounds. A nother therapeutic target is the peroxisome proliferator-activated receptor (PPAR). PPARs are nuclear hormone transcription factors that regulate genes associated with lipid and glucose metabolism. A s such, PPAR agonists have demonstrable efficacy in lowering blood glucose in diabetes\textsuperscript{98}. They also appear to have anti-inflammatory effects. Wang and colleagues\textsuperscript{100}
have shown that activation of PPAR-γ receptor reduced the cytokine-induced expression of the inducible form of nitric oxide synthase in a dose-dependent manner and reduced epithelial cell secretion of interleukin (IL)-8. PPAR-γ ligands also appear to downregulate inflammatory activities in airway smooth muscle cells and to inhibit their proliferation101.

Summary

It is increasingly clear that COPD is a highly preventable and treatable condition. Bronchodilators provide symptomatic relief, while anti-inflammatory medications may modify the natural course of the disease. There are many compounds in development, targeting a variety of different inflammatory pathways that offer great promise as therapeutic agents in COPD. However, it will take several years before these promising drugs become available in the market. In the meantime, physicians should continue to emphasize the importance of smoking cessation to COPD patients and provide pharmacologic and non-pharmacologic treatments to those who are symptomatic from their disease.

References


4) SULLIVAN SD, RAMSEY SD, LEE TA. The economic burden of COPD. Chest 2000; 117(2 Suppl): SS-9S.


17) FIORE MC. Treating Tobacco Use and Dependence: A Public Health Service Clinical Practice Guideline. Center for Tobacco Research and Intervention, University of Wisconsin Medical School.
Treatment of COPD


41) SIN DD, MANFREDA FA, MA PN, ANTHONIEN NR. Contemporary management of chronic obstructive pulmonary disease: scientific review. JAMA 2003; 290: 2301-2312.


Acknowledgements

Funding Support: DDS is supported by a Canada Research Chair (Respiration) and a Michael Smith/St. Paul’s Hospital Foundation Professorship in COPD. This research was in part funded by the Canadian Institutes of Health Research.