

Treatment of mild chronic obstructive pulmonary disease

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Abstract: Chronic obstructive pulmonary disease (COPD) is an epidemic in many parts of the world. Most patients with COPD demonstrate mild disease. The cornerstone of management of mild disease is smoking cessation, which is the only proven intervention to relieve symptoms, modify its natural history and reduce mortality. For asymptomatic patients, it is the only required therapy. Short-acting bronchodilators can be added on an as needed basis for those with intermittent symptoms and regularly for those with persistent symptoms. Long-acting bronchodilators can be substituted for those who remain symptomatic despite regular use of short-acting bronchodilators. Inhaled corticosteroids do not modify the natural history of COPD and as such cannot be recommended as standalone therapy for mild COPD. However, for patients with refractory and intractable symptoms, they may be used in combination with long-acting beta-2 agonists. Influenza and pneumococcal vaccination and pulmonary rehabilitation are other therapies that may be considered for select patients with mild disease. In this paper, we summarize the current standard of care for patients with mild COPD.

Keywords: COPD, management, mild COPD

Introduction

Chronic obstructive pulmonary disease (COPD) is an inflammatory disorder of the lung that is characterized by irreversible or partially reversible airflow limitation (Rabe et al 2007). It is highly prevalent affecting 600 million people worldwide and accounting for nearly 4 million deaths annually (Murray and Lopez 1997b). Over the next 20 years, the burden of COPD is expected to increase, making it the third leading cause of mortality worldwide (currently fourth) (Murray and Lopez 1997a). COPD is a relentless and progressive disease, caused by a complex interaction between genes and environment. Although cigarette smoking is the single most important risk factor, smokers constitute only ~50% of the worldwide cases of COPD; the rest occur in life-time never smokers (Mannino and Buist 2007). Furthermore, once COPD develops, smoking cessation does not abrogate the increased risk of morbidity and mortality (though the risk is smaller than when they were actively smoking) (Anthonisen et al 2005; Pelkonen et al 2000; Sin et al 2005b) and smoking cessation does not halt the underlying inflammatory process in the lungs of COPD patients (Willemse et al 2005). Other known risk factors for COPD include airway hyperresponsiveness, genetic abnormalities such as alpha-1-antitrypsin deficiency, air pollution, biomass smoke exposure, occupational dusts and chemicals, respiratory infections especially during childhood, and poor nutrition (Chapman et al 2006). Unfortunately, there is a dearth of therapies that can effectively modify disease activity or progression. The current treatment is largely aimed at relieving patient symptoms and reducing long-term complications (Sin et al 2003) and is modified by disease severity (Rabe et al 2007).

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The management algorithms for moderate to severe COPD have been reviewed expertly elsewhere (Sin et al 2003; Wilt et al 2007). In this paper, we will review the management goals and strategies for patients with mild COPD.

Definition of mild COPD

COPD is diagnosed clinically based on history and physical examination, complemented by spirometric data demonstrating irreversible or poorly reversible airflow obstruction in the absence of an alternate diagnosis such as congestive heart failure, neuromuscular disease or asthma (Man et al 2003). Most but not all patients with COPD are either current or ex-smokers with at least 10 pack-year smoking history (pack-years is calculated by multiplying the number of cigarettes smoked per day by the years smoked divided by 20). The most common presenting symptom is dyspnea with exertion or chronic cough with or without sputum production. Other (but more infrequent) symptoms include chest pain, orthopnea and wheezing. However, there is also a group of patients with abnormal spirometry but are otherwise asymptomatic. The physical examination is completely unremarkable in most patients with mild COPD. In some cases, however, patients may demonstrate a positive cough test (which is defined as recurrent coughing after patients take a deep breath to maximal lung capacity and coughs more than once), and have a forced expiratory time at the bedside of 9 seconds or greater (Straus et al 2000). On spirometry, patients with COPD demonstrate a forced expiratory volume in one second (FEV₁) to forced vital capacity (FVC) ratio of less than 0.70 following receipt of a bronchodilator (eg, albuterol 200–400 µg

(O'Donnell et al 2007; Rabe et al 2007). Once the diagnosis of COPD is made, severity is assessed using the post-bronchodilator FEV₁ value. An example of the severity classification scheme is shown in Figure 1 (O'Donnell et al 2007). Mild COPD is defined by a post-bronchodilator FEV₁ that is 80% of predicted or greater in the presence of an FEV₁/FVC ratio of less than 70% and characteristic symptoms such as exertional dyspnea in most cases (Celli and MacNee 2004; Rabe et al 2007). However, some who meet the spirometric criteria of mild COPD may be asymptomatic. In one study of patients who were seen at a primary care office, over a third of ex- and current smokers who were diagnosed with mild COPD based on screening spirometry were asymptomatic at the time of testing, while 2/3 of never smokers diagnosed with mild COPD were asymptomatic (Bednarek et al 2008). Thus, the prevalence of COPD based on physician or self-diagnosis likely under-estimates the prevalence of COPD based on spirometry (Buist et al 2007). A more liberal use of spirometry in primary care may increase the detection and diagnosis of COPD in the community.

Treatment goals

Although patients with mild COPD are at increased risk of respiratory infections and respiratory failure, COPD-related hospitalizations and deaths are relatively infrequent in this group of patients (Anthonisen et al 1994). Thus, dissimilar to those with more severe disease, prevention of respiratory complications such as exacerbations and respiratory mortality is not the primary goal in the treatment of mild COPD. Instead, treatment goals are focused on the following 3 domains: 1) relieving patient symptoms;

Stage 1 Mild	Stage 2 Moderate	Stage 3 Severe	Stage 4 Very Severe
<p>FEV₁ ≥ 80% predicted</p> <p><i>Asymptomatic or short of breath when hurrying on the level or walking up a slight hill</i> MRC 2</p>	<p>FEV₁ 50 to 79% predicted</p> <p><i>Short of breath causing the patient to stop walking on the level 100 metres (or after a few minutes)</i> MRC 3 to 4</p>	<p>FEV₁ 30 to 49% predicted</p> <p><i>Too short of breath to leave the house, breathless dressing or undressing</i> MRC 5</p>	<p>FEV₁ ≤ 30% predicted <i>or</i> <i>chronic respiratory failure</i> <i>or</i> <i>right heart failure</i></p>

From Global Initiative for Obstructive Lung Disease disease categories and Canadian Thoracic Society COPD guidelines. All stages require a FEV/FVC ratio of <0.70.

Figure 1 COPD Severity Classification Scheme Copyright © 2007. Reproduced with permission from O'Donnell DE, Aaron S, Bourbeau J, et al 2007. Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease – 2007 update. *Can Respir J*, 14(Suppl B):5B–32B.

2) slowing the progression of disease; and 3) mitigating the risk for cardiovascular disease (CVD) and lung cancer, which are the leading causes of hospitalization and mortality in patients with mild COPD (Anthonisen et al 1994).

Treatment goal 1: relief of patient symptoms

The most common symptom in mild COPD is exertional dyspnea with or without chronic cough. In assessing these symptoms, physicians must rule out all other causes of dyspnea including cardiovascular de-conditioning, neuromuscular disease, interstitial lung disease, ischemic heart disease, congestive heart failure, pulmonary embolism, anemia and pulmonary hypertension. A careful history and physical examination, accompanied by simple laboratory tests such as pulse oximetry, chest radiograph, electrocardiogram, complete blood count and spirometry are usually sufficient in excluding other common causes of dyspnea. In a minority of cases, additional tests including incremental cardiopulmonary exercise testing, echocardiogram and computed tomography (CT) may be necessary. Once all causes of dyspnea have been ruled out and COPD is confirmed by spirometry, management can be initiated.

Smoking cessation

Symptomatic treatment starts with smoking cessation for smokers with mild COPD. In a dose dependent manner, smoking induces cough and dyspnea and smoking cessation attenuates these symptoms (Stein et al 2005). Although the prevalence of smoking has declined over the past two decades in the US and other industrialized nations, 20% of adults in the western world continue to smoke. In the developing world, smoking rates are increasing with nearly 40% of adults smoking on a daily basis in certain jurisdictions (Ezzati and Lopez 2003). Although clinicians should encourage patients to stop smoking and provide practical advices in their clinic, these measures are generally ineffective, leading to smoking cessation in only about 5% of smokers (Bailey 1985). This intervention, however, is more effective when offered at the time the diagnosis of COPD is made (Stratelis et al 2006). Another way to increase cessation rate is to convey the concept of "lung age" to the patients. Lung age is defined as the age of the average person who has the same FEV₁ as that of the patient and can be calculated using the formula: lung age (for men) = $2.87 \times \text{height (in inches)} - 31.25 \times \text{observed FEV}_1 \text{ (liters)} - 39.375$ and lung age (for women) = $\text{age} = 3.56 \times \text{height (in inches)} - 40 \times \text{observed FEV}_1 \text{ (liters)} - 77.28$ (Morris and Temple 1985). In the largest randomized trial of its kind, Parkes et al showed that smokers

who received information regarding their "lung age" were twice as more likely to quit than smokers who received their raw FEV₁ data (Parkes et al 2008). At 12 months of follow-up, the cessation rate was 14% in the lung age group versus 6% in the control group.

Comprehensive smoking cessation clinics consisting of physician services, cognitive and behavioral modification programs, and nicotine replacement therapy achieve the best results (Schroeder 2005). Cognitive programs employ techniques such as distraction, positivism, relaxation, and mental imagery to modify patient's attitude towards smoking (Schroeder 2005). Behavioral interventions, on the other hand, focus on breaking the smoking habit by avoiding smoking triggers such as drinking coffee or alcohol or associating with friends who smoke. Collectively, these methods are effective in fostering quitting in about 10% to 15% of motivated smokers (Kanner et al 1999).

One of the cornerstones in smoking cessation is the use of nicotine replacement therapy (NRT). NRT has been expertly reviewed elsewhere (Molyneux 2004). The major goals of NRT are to 1) attenuate withdrawal symptoms, 2) eliminate craving; and 3) make smoking less rewarding. NRT generally doubles the cessation rate compared to physician advice alone (Molyneux 2004). High doses of NRT are more effective than lower doses but are fraught with more side effects (Schroeder 2005). However, for those patients refractory to the lower doses, higher doses should be considered. Side effects include insomnia, skin irritation (for patches), and early morning cravings for nicotine. There are 6 ways in which NRT can be administered: as a patch, gum, sublingual tablet, lozenge, nasal spray, or inhaler. The patches are the most common mode of delivery and are found in 16-hour (5, 10, 15 mg) or 24-hour (7, 14, 21 mg) formulations. The gums are also frequently used and they are packaged in 2- or 4-mg pieces.

Non-nicotine based pharmacologic therapies are also available and are as effective as NRT in fostering smoking cessation. Anti-depressants and in particular bupropion significantly enhance cessation rates. Similar to NRTs, bupropion and nortryptyliline double the quitting rates compared with advice alone (Hughes et al 2007). Bupropion should be prescribed at least 1 week before the cessation date, so that adequate blood levels can be achieved and continued for 2 to 3 months following cessation. There is insufficient evidence to determine whether or not anti-depressants provide incremental benefits on cessation beyond that achieved by NRT alone. Serious side effects from anti-depressants are relatively uncommon. The risk of seizures is about 0.1% with the

use of bupropion (Hughes et al 2007). Thus, bupropion should be avoided in patients with a seizure disorder (Schroeder 2005). Although there are ongoing concerns regarding the possible increased risk of suicides among those who take bupropion, there is insufficient body of evidence to support this notion.

More recently $\alpha 4\beta_2$ nicotinic acetylcholine receptor agonists (eg, varenicline) have been introduced into the market for smoking cessation (Gonzales et al 2006). Varenicline is a partial $\alpha 4\beta_2$ nicotinic receptor agonist. It is approximately three times more effective in effecting smoking cessation than is placebo (Cahill et al 2007). It should be started at 0.5 mg daily while the patient is still smoking and then escalated to 1 mg per day by the second week. The patient should quit smoking completely by week 2 and the drug should be continued for another 12 weeks. The most common side effect of this drug is nausea, which can be mitigated by taking the drug following meals. Varenicline appears to be more effective than bupropion (odds ratio for smoking cessation, 1.66) (Cahill et al 2007). However, it should be used with extreme caution (if at all) in patients with a past history of severe depression or a psychosis as it has been rarely associated with major psychiatric adverse effects (Pumariega et al 2008).

Bronchodilators

For those who remain symptomatic despite smoking cessation, bronchodilators may be used to improve patient symptoms. If the symptoms are periodic, short-acting bronchodilators (eg, beta-2 agonists or anticholinergics) can be used on an as-needed basis. For those with persistent symptoms, short-acting bronchodilators may be used regularly (eg, 4 times a day) or, alternatively, long-acting bronchodilators may be used instead. All bronchodilators work by increasing expiratory flow, reducing dynamic hyperinflation and improving exercise capacity and quality of life of patients (Hanania and Donohue 2007). However, the improvement in symptoms and exercise capacity is not readily predictable from the spirometric response to bronchodilators. There are two major classes of bronchodilators: β_2 -agonists and anti-cholinergic agents.

β_2 -agonists

All β_2 -agonists act by binding to and stimulating cell surface β_2 -adrenoceptors, which belong to a seven transmembrane G-protein coupled receptor family. Upon ligand binding, the α -component of the G-protein dissociates and activates adenylate cyclase (Johnson 1998), which in turn stimulates the production of cyclic adenosine monophosphate, and

activates protein kinase A (PKA). PKA then phosphorylates a number of intracellular regulatory proteins (Johnson 1998). Stimulation of the β_2 -adrenoceptors can also inhibit histamine and cysteinyl-leukotriene release from mast cells, prevent plasma exudation from postcapillary venules, and modulate sensory neural outputs in the airways (Johnson 1998). Thus, in addition their bronchodilatory properties, β_2 -agonists may have anti-inflammatory effects.

There are two major categories of β_2 -agonists: short acting β_2 -agonists (SABA) and long-acting β_2 -agonists (LABA). SABAs have a rapid onset of action (1–3 minutes) and their pharmacologic effects last less than six hours (Rabe et al 2007). Thus, they provide quick relief of dyspnea and are best used as rescue medications for patients with intermittent symptoms. In patients with persistent symptoms, regular use of SABAs (usually four times a day) either alone or in combination (of β_2 -agonist and anticholinergic) is recommended. Of the SABAs, salbutamol (albuterol) is the most commonly used agent and can be delivered via a metered dose inhaler or a nebulizer. For patients with mild COPD who have symptoms refractory to SABAs, LABAs may be considered. The two most commonly used LABAs in clinical practice are salmeterol and formoterol. Both of these compounds have high affinity for β_2 -adrenoceptors. Salmeterol is considered a partial agonist because the ligand-receptor coupling is incomplete. In contrast, formoterol binds completely to the β_2 -adrenoceptor, making it a full agonist. Salmeterol binds to β_2 -adrenoceptor in airway smooth muscle with an efficacy of 65% compared to formoterol (Ball et al 1991). Despite these differences, clinically, they appear to have similar effectiveness. On average, formoterol provides faster relief of symptoms than does salmeterol but salmeterol may provide longer duration of relief (Johnson, 1998). Although some safety concerns have been raised regarding their use in asthma (Martinez 2005; Salpeter et al 2006), LABAs appear to be safe in COPD (Calverley et al 2007).

Anticholinergics

Anticholinergic agents, on the other hand, reduce airway tone by blocking the muscarinic receptors that induce bronchial smooth muscle contraction. Ipratropium bromide is the prototypical short acting anticholinergic agent, which has a half-life of less than 6 hours (Rabe et al 2007). Tiotropium is a longer acting anticholinergic agent that is approximately 10-fold more potent than ipratropium bromide. This is because tiotropium dissociates very slowly from lung muscarinic receptors and in airway smooth muscles demonstrates partial

selectivity for the M3-receptors. Clinically, tiotropium provides bronchodilation for greater than 24 hours and thus is suitable for once-daily dosing (Barnes et al 1995).

Tiotropium has been largely tested in patients with moderate to severe disease. Clearly, in moderate to severe disease, tiotropium reduces patient symptoms, improves health-related quality of life, reduces exacerbations (Barr et al 2006), decreases dynamic hyperinflation of the lungs (Maltais et al 2005) and increases exercise tolerance (Casaburi et al 2005). However, there is little information on the effectiveness of tiotropium in patients with mild disease. In one 12-week randomized controlled trial (N = 224; mean FEV₁, 74% of predicted), patients with mild COPD who received tiotropium experienced a 118 mL improvement in FEV₁ and required fewer daily doses of a short-acting β₂-agonists compared to those who received placebo (Johansson et al 2008). However, symptom and quality of life scores were no different between the two groups.

Similarly, there is a large body of evidence indicating that LABA is effective in relieving symptoms and improving health status in patients with moderate to severe COPD (Calverley et al 2007; Sin et al 2003). However, as with tiotropium, there is a marked scarcity of information regarding their effectiveness in mild COPD. In general, while they improve lung function, they do not appear to have a major impact on patient symptoms or quality of life in mild COPD (Appleton et al 2006). Thus, LABAs cannot be recommended routinely for mild COPD except in patients who have persistent symptoms despite SABAs or in those who have frequent exacerbations requiring systemic corticosteroid therapy and/or hospital visits.

Inhaled glucocorticoids

Inhaled glucocorticoids have been used for COPD over the past 3 decades. Nevertheless, their exact role in COPD management remains uncertain. In the 1990s, several large-scale randomized controlled trials were conducted to clearly define the benefits and the hazards of inhaled corticosteroids in the treatment of COPD. All of these studies were powered to determine whether or not inhaled corticosteroids modified the rate of decline in FEV₁. However, several studies also captured the effects of these drugs on patient symptoms. In one of the largest study of its kind, the Lung Health Study (LHS)-2 evaluated the effects of inhaled triamcinolone on symptoms in patients with mild to moderate COPD (mean FEV₁, 68% of predicted) (Lung Health Study Group, 2000). On average, the subjects were followed for 40 months. Triamcinolone had no significant effect on cough

and sputum production (p = 0.26) but a significant impact in reducing dyspnea (p = 0.02). Sixty-eight percent of patients in the triamcinolone arm did not complain of dyspnea by the end of the study, while 62% did not have dyspnea in the placebo arm (a difference of 6.7%). Importantly, compared with placebo, there was a 29% relative reduction in the number of patients who complained of difficulty breathing (p = 0.05), and a 35% relative reduction in the number of patients with wheezing in the group that took triamcinolone (Lung Health Study Group, 2000). In the Copenhagen City Heart Study (mean FEV₁, 87% of predicted), similar to LHS-2, inhaled budesonide did not have a significant impact on cough and sputum production (Vestbo et al 1999). Collectively, these data suggest that inhaled corticosteroids probably do not have any significant effect on cough and sputum production; they appear to have a modest effect in reducing dyspnea. However, in view of the long-term safety concerns associated with inhaled corticosteroids including bone demineralization and skin bruising, they cannot be routinely recommended in patients with mild COPD. Inhaled corticosteroids may be considered for patients with dyspnea refractory to smoking cessation and bronchodilators.

Pulmonary rehabilitation

In COPD, patients experience dyspnea and exercise limitation because of impaired gas exchange, increased dead space ventilation and dynamic hyperinflation (Ofir et al 2008). Additional demands are placed on the respiratory system by physical deconditioning and peripheral muscle dysfunction. Exercise training programs in COPD have the goal of improving cardiovascular fitness, increasing aerobic capacity of muscles and decreasing symptoms. Pulmonary rehabilitation programs have also been shown to decrease the number of exacerbations and shorten the length of hospital stay during an exacerbation (Hunter and King 2001; Nici et al 2006). Although most of these studies were conducted in patients with moderate to severe disease, several studies were evaluated patients with mild COPD (Bianchi et al 2002; Clark et al 2000; Durado et al 2006; Garrod et al 2004; Kamahara et al 2004; Karapolat et al 2007; Rossi et al 2005). Clinical outcomes were measured by activity endurance (6 minute walk test) as well as with a quality of life instrument such as the St Georges Respiratory Questionnaire (SGRQ). One study found that muscle function and oxygen utilization (VO₂max, VTmax, paired t-test) improved after a 12-week rehabilitation program involving isokinetic strength training (Clark et al 2000), while another showed improved exercise endurance with pulmonary rehabilitation (R² = 0.146) (Eakin et al 1992).

However, the beneficial effects of pulmonary rehabilitation appear to be time-limited and wears off over time unless the exercise program is continued (Karapolat et al 2007). Additionally, pulmonary rehabilitation programs that are longer in duration appear to be superior to short programs. One study found that a 20-session course led to improved 6 minute walk distance and better quality life compared with a 10-session course. Thus, pulmonary rehabilitation program should be considered for patients with mild COPD, who are symptomatic and are experiencing limitations in activity endurance and reduced quality of life.

Independent of symptoms all patients should be encouraged to exercise regularly (low to moderate intensity exercise for 30 minutes greater, at least 3 to 4 times per week) as regular physical activity independent of other factors is associated with slower progression of disease (Garcia-Aymerich et al 2007). Additionally, patients should receive dietary counseling to ensure that adequate amount of calories are consumed each day and the diet is enriched for fruits, vegetables and fish, which may decrease COPD progression (Varraso et al 2007).

Treatment goal 2: slow the progression of disease

Smoking cessation

The most commonly used metric for measuring disease progression in COPD is the rate of decline in lung function, as assessed by FEV₁. Due to the intrinsic variability of the measurement, at least 3 FEV₁ values measured over 3 years are needed to adequately assess progression. It is well known that smoking accelerates the decline in FEV₁, while smoking cessation normalizes the rate of decline. In the Lung Health Study, which evaluated 5,800 smokers with mild to moderate COPD, smokers who continued to smoke lost on average 60 mL/year in FEV₁ over a 5 year follow-up period. In contrast, sustained quitters lost 14 mL/year in FEV₁ (Anthonisen et al 1994). Over 11 years of follow-up, sustained quitters lost 26 to 30 mL/year (or 0.23% to 0.40% of predicted/year) in FEV₁, whereas intermittent quitters lost 48 to 50 mL/year (or 0.91% to 1.02% of predicted/year) and continued smokers lost 60 to 64 mL/year (or 1.29 to 1.44% of predicted/year) in FEV₁ (Anthonisen et al 2002). Smoking cessation is the only proven method of retarding disease progression in COPD.

Inhaled glucocorticoids

In the 1990s, there was renewed enthusiasm for using inhaled corticosteroids to modify the natural history of COPD

(Sin et al 2005a). Several long-term randomized controlled trials were performed in mostly mild to moderate COPD subjects. Collectively, these trials indicated that within the first 6 months of therapy, inhaled corticosteroids increased FEV₁ compared to placebo. The effect was most pronounced in female non-smokers. However, they did not modify the long-term decline in FEV₁ (Soriano et al 2007).

Combination of inhaled glucocorticoids and LABAs

In moderate to severe COPD, LABAs and inhaled corticosteroids either by themselves or in combination have a modest effect on disease progression. In the TORCH (TOWards a Revolution in COPD Health) Study, which evaluated these medications in moderate to severe COPD, patients who received inhaled fluticasone or salmeterol experienced a slower decline in FEV₁ (by 13 mL/year) compared to those who received placebo (Calverley et al 2007). Patients who received a combination of fluticasone and salmeterol demonstrated the slowest decline (by 16 mL/year). The effects of tiotropium on disease progression have been assessed in the UPLIFT trial (Understanding the Potential Long-Term Impacts on Function with Tiotropium) (Decramer et al 2004). The findings of this trial are expected in the fall of 2008.

Treatment goal 3: reduce the risk of CVD and lung cancer related morbidity and mortality

In the Lung Health Study, which studied patients with mild to moderate COPD, the leading cause of hospitalization were CVDs, accounting for nearly 50% of all hospitalizations (Anthonisen et al 1994). Although deaths were rare, over 20% of all deaths were CVD in nature. In the National Health Examination Follow-up Survey, which sampled a representative mix of the US civilian adult population, baseline FEV₁ was independent predictor of CVD hospitalization and mortality over 10 years of follow-up. Even within the "normal ranges" of FEV₁ values, individuals who had the highest FEV₁ were least likely to develop CVDs (see Figure 2), while those with reduced FEV₁ values had higher risk of CVD (Sin et al 2005b). Mild COPD is associated with a 2-fold increased risk of CVD compared to individuals without COPD (Sin et al 2005b). Similarly, the risk of lung cancer is increased in mild COPD (Wasswa-Kintu et al 2005). Indeed, lung cancer is the most common cause of death in mild COPD, accounting for 1/3 of

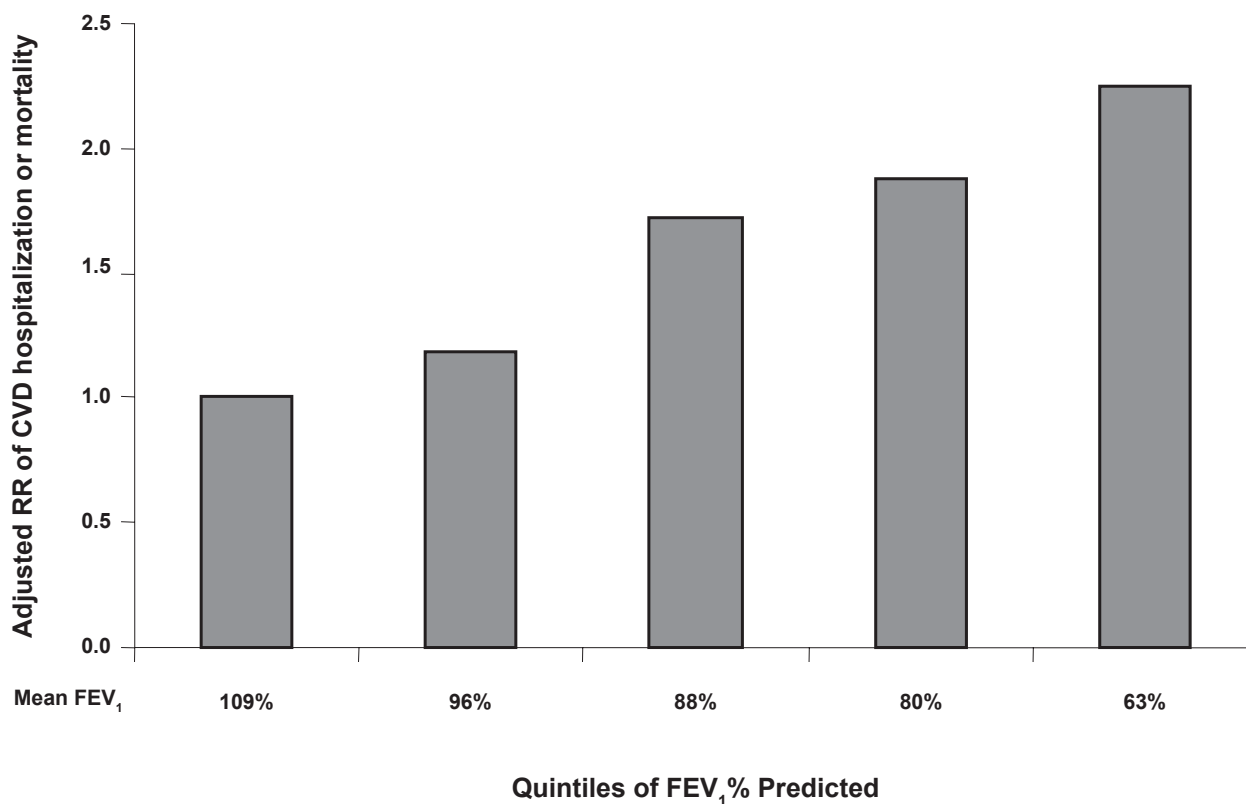


Figure 2 The relationship between forced expiratory volume in one second (FEV₁) and cardiovascular mortality or hospitalization in the First National Health Nutrition and Examination Survey (derived from Sin et al 2005b).

The Y-axis plots the relative risk of cardiovascular disease (CVD) hospitalization or mortality in subjects who participated in the NHANES I study. The x-axis plots the group in quintiles of FEV₁ and the mean FEV₁ value is shown for each of the quintile.

all deaths in this group of patients (Anthonisen et al 1994). The mechanisms by which mild COPD increase the risk of CVD and lung cancer are still a mystery. Inflammation, oxidative stress, DNA mutation and shared risk factors are some of the common explanations.

Smoking cessation

Smoking cessation is the only proven way of reducing CVD and lung cancer in COPD patients. CVD risk is particularly responsive to smoking cessation. Compared to continued smokers, CVD mortality is reduced by over 60% in sustained quitters (Anthonisen et al 2005). Interestingly, the CVD mortality risk is reduced by 54% even among intermittent quitters. In contrast, the risk of lung cancer mortality is only reduced by 20% among intermittent quitters compared to continued smokers, although it is reduced by ~55% in sustained quitters (see Figure 3).

Glucocorticoids

Inhaled corticosteroids may modify long-term risk of CVD and lung cancer in patients with COPD. Using a large

health administrative database from Veterans Affairs, Parimon and colleagues reported that inhaled corticosteroids ($\geq 1200 \mu\text{g/day}$ of triamcinolone, which is equivalent to $\geq 180 \mu\text{g/day}$ of beclomethasone) were associated with a 61% reduction in the risk of lung cancer (Parimon et al 2007). In a randomized control trial, Lam and colleagues evaluated the effects of inhaled budesonide on bronchial dysplasia in 113 smokers (with relatively normal lung function) over 6 months. Although there was no significant effect of inhaled budesonide on disease progression, it significantly reduced prostaglandin E₂ levels in the bronchoalveolar lavage fluid and expression of p53 and BCL-2 in bronchial tissues. Inhaled budesonide also reduced the number of pulmonary nodules detected on computed tomographic (CT) scans (Lam et al 2004). In the Inhaled Steroid Effects Evaluation in COPD (ISEEC) study, which was a pooled analysis of 7 large trials of inhaled corticosteroids in COPD, there was a trend towards lower cancer mortality in the group that received corticosteroids compared with placebo (relative risk, 0.55; 95% confidence interval, 0.29 to 1.03)

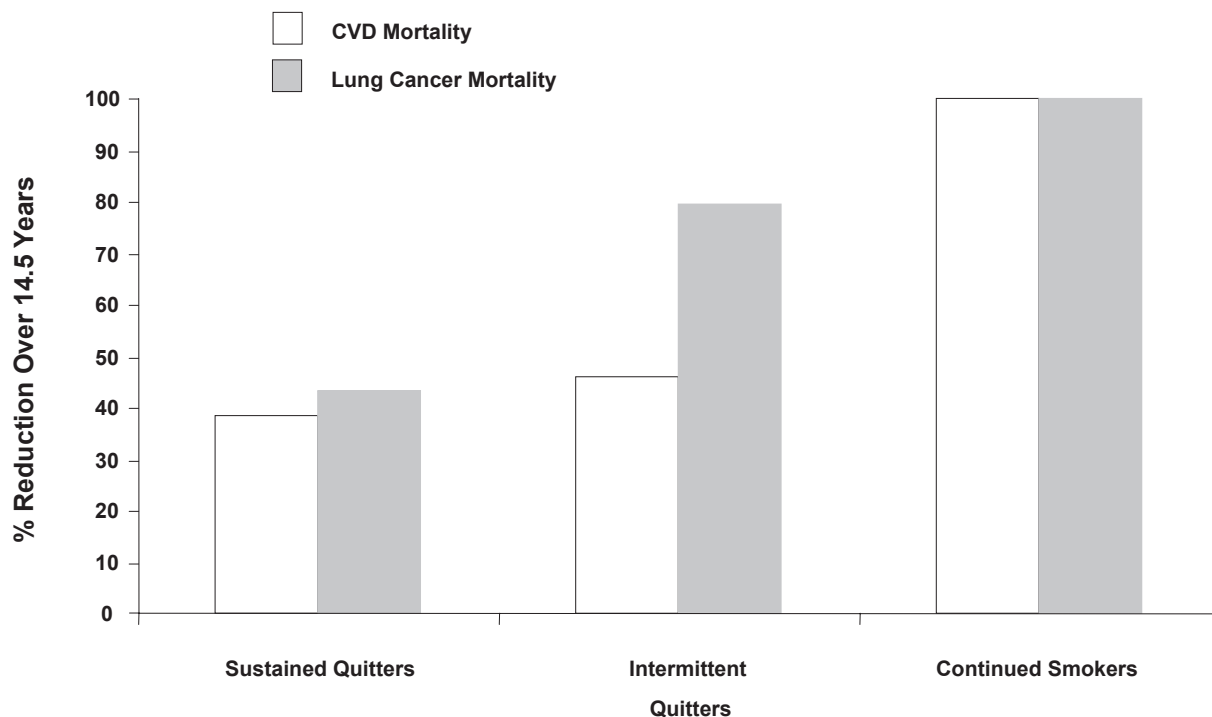


Figure 3 The effect of smoking cessation on cardiovascular and lung cancer mortality (derived from Anthonisen et al 2005).

The Y-axis plots the relative risk reduction in mortality from each of the causes relative continued smokers. Sustained quitters are defined as those who stopped smoking entirely during the follow-up period. Intermittent quitters are those who quit and re-started smoking.

(Sin et al 2005a). Long-term large-scale trials are needed to confirm these early observations and determine the effects of inhaled corticosteroids on lung cancer in COPD patients.

Inhaled corticosteroids have also been associated with reduced risk of CVD. Huiart and colleagues, using a large administrative database from Saskatchewan, reported that COPD patients who used 50 to 200 µg/day of beclomethasone (or equivalent) were 32% less likely to experience myocardial infarction than those who did not use any inhaled corticosteroids (Huiart et al 2005). Macie and colleagues, using another large administrative database from Manitoba, showed that COPD patients who used inhaled corticosteroids were nearly 40% less likely to suffer a cardiac mortality than those who did not (Macie et al 2006). In EUROSCOP (European Respiratory Society's study on Chronic Obstructive Pulmonary Disease), 1,277 patients with mild to moderate COPD (mean FEV₁, 77% of predicted) were assigned to inhaled budesonide or placebo for 3 years. A post hoc analysis of the safety data demonstrated that patients assigned to inhaled budesonide had 42% fewer ischemic cardiac events (defined as angina pectoris, myocardial infarction, coronary artery disease, or myocardial infarction) compared to those assigned to placebo ($p = 0.048$) (Lofdahl et al 2007). However, these data must be interpreted cautiously because the baseline event rate was low (4.2%).

Vaccination

COPD independently contributes to mortality and increased length of stay in hospitals from community-acquired pneumonia (Restrepo et al 2006). Influenza vaccination reduces overall mortality by 70% in patients with chronic lung disease (odds ratio 0.30, $p < 0.001$) (Nichol et al 1999a). However, it does not appear to modify the rate of exacerbations in patients with mild COPD (Menon et al 2008; Poole et al 2006). Pneumococcal vaccination is also associated with reduced risk of hospitalizations from pneumonia as well as all-cause mortality beyond that achieved with influenza vaccination (Nichol et al 1999b).

Summary and conclusion

COPD is a treatable disease. A short synopsis of a management strategy for mild COPD is provided in Table 1. The cornerstone of management is smoking cessation, which not only improves patient symptoms but is the only proven way of modifying its natural history and reducing mortality. Vaccinations for influenza and pneumococcus may reduce morbidity and mortality from community-acquired pneumonia. In patients who have intermittent symptoms, short-acting bronchodilators may be used on an "as-needed" basis, while for patients with more persistent symptoms, these drugs

Table 1 Management algorithm for mild COPD

	Asymptomatic	Intermittent symptoms	Persistent symptoms	Refractory symptoms
Smoking cessation	X	X	X	X
Short-acting bronchodilators		X ^a	X ^b	X
Long-acting bronchodilators			X ^c	X
Inhaled glucocorticoids				X ^d

^ause on an as-needed basis.

^buse on a regular basis (eg, 4 times a day).

^cuse in cases where patients remain symptomatic despite regular use of short acting bronchodilators.

^dinhaled glucocorticoids may be added if patients remain symptomatic despite the regular use of long-acting bronchodilators. Inhaled glucocorticoids probably should not be used in by themselves.

may be given regularly (eg, 4 times a day). In patients whose symptoms are refractory to short-acting bronchodilators, long-acting bronchodilators may be provided. LABAs and tiotropium appear to have similar effectiveness for patients with mild disease. Pulmonary rehabilitation regimens may also improve exercise tolerance and quality of life. In a small minority of patients who remain symptomatic despite long-acting bronchodilators, a combination of inhaled corticosteroids and LABAs may be considered. Although inhaled corticosteroids by themselves reduce dyspnea and improve lung function, they probably should not be the sole therapy for patients with mild disease in view of their potential long-term side effects. Inhaled corticosteroids do not appear to modify the long-term decline in FEV₁; however, there are emerging data suggesting their potential usefulness in reducing the risk of lung cancer and CVD, which are the leading causes of mortality and hospitalization in mild COPD. However, before this notion can be fully accepted, large-scale randomized controlled trials are needed to validate these early findings.

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