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REVIEW

Maintenance pharmacotherapy of mild and moderate COPD: What is the Evidence?

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Summary
Chronic obstructive pulmonary disease (COPD) affects more than 24 million individuals in the United States, although at least half of the cases are not diagnosed. Proactive diagnosis and limitation of risk exposure from smoking or pollutants are important to improve prognosis. Pharmacologic treatments are prescribed according to COPD stage and symptoms. Mild COPD is symptomatically treated 'as needed' with short-acting bronchodilators; major guidelines recommend starting maintenance treatment at the moderate COPD stage with long-acting bronchodilators; inhaled corticosteroids may be added for patients with more severe disease and frequent exacerbations. Maintenance therapy preserves 24-h airway patency, reduces exacerbations, and improves activity tolerance and health-related quality of life. Recent post-hoc analyses of large clinical trials that contain subgroups of patients with less severe COPD suggest that, similar to those with advanced disease, patients with moderate disease benefit from long-term maintenance therapies. Studies suggest symptomatic mild patients may also benefit. This concept needs to be prospectively tested in studies specific to these COPD disease stages. Proactive identification and pharmacologic intervention in early COPD has the potential to alter clinical outcomes throughout the disease course.

Contents

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Introduction

Chronic obstructive pulmonary disease (COPD) is defined as a preventable and treatable disease characterized by airflow limitation that is not fully reversible. The most common symptoms of COPD include chronic cough, sputum production, and dyspnea with exertion.[1] Other less specific symptoms may include fatigue, weight loss, edema, chest tightness, and sleep disturbances.[2] Exertional dyspnea in patients with COPD often reflects dynamic lung hyperinflation that worsens with increasing airway obstruction.[3] Cardiac comorbidities and/or COPD-related cardiac dysfunction may also be contributing factors to dyspnea.[4,5]

COPD is a major cause of morbidity and mortality worldwide, affecting over 210 million individuals.[6] The World Health Organization estimates that COPD will be one of the four leading causes of death in 2030.[7] In 2007, over 12 million adults in the United States were diagnosed with COPD,[8] with epidemiologic studies estimating that an additional 12 million adults remain undiagnosed.[8,9] This undiagnosed population consists mainly of adults with mild-to-moderate COPD. Indeed, a recent study of a general practice population assessing current and former smokers over the age of 40, without any prior diagnosis or treatment for airways disease, determined the prevalence of COPD to be 19%.[10] Among these newly identified COPD patients, 57% had mild, 37% had moderate, and 6% had severe disease. Patients with symptoms associated with COPD often do not seek medical attention until the symptoms interfere with their quality of life, which typically occurs in more severe disease.[11] On the other hand, patients early in the course of COPD often have significant symptoms, even in the absence of marked spirometric dysfunction. This may be due, in part, to disproportionate ventilatory demands, decreased inspiratory capacity with dynamic hyperinflation, and ventilation-perfusion mismatching during exercise.[3] Finally, many patients with respiratory symptoms are diagnosed with asthma and only later recognized as having COPD.[12]

Spirometry is essential to the diagnosis and staging of COPD. All major society guidelines require the demonstration of airflow limitation, defined as a post-bronchodilator forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio of <0.7, as essential to the diagnosis of COPD.[1,13,14] Although many aspects of COPD impact on disease severity, current staging of COPD disease severity is based on the presence of airflow limitation ($FEV_1/FVC < 0.7$) and the degree of airflow impairment as determined by the value of FEV_1, expressed as a percent of predicted. Disease severity, as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) and the American Thoracic Society and European Respiratory Society (ATS/ERS), is as follows: mild COPD (*Stage I*), $FEV_1 \geq 80\%$ of predicted; moderate COPD (*Stage II*), $50\% \leq FEV_1 < 80\%$ of predicted; severe COPD (*Stage III*): $30\% \leq FEV_1 < 50\%$ of predicted; and very severe COPD (*Stage IV*): $FEV_1 < 30\%$ of predicted or findings of chronic respiratory failure. Interestingly, guidelines from the Canadian Thoracic Society[14] now use symptoms and other functional parameters to assess severity rather than relying solely on spirometry results, and recommend using dyspnea, as measured by the Medical Research Council dyspnea index, to also guide staging and treatment.[14]

Although most patients present for medical evaluation when the severity of COPD has increased, earlier diagnosis allows for added smoking cessation efforts, which may increase smoking cessation rates,[15] leading to a greater impact on disease progression and perhaps even reduced mortality. Indeed, the classic Fletcher–Peto diagram of lung function decline with time (Fig. 1A) shows the impact of smoking cessation initiated at earlier stages of the disease on airflow obstruction, delaying or preventing severe airflow obstruction and its consequences.[16]

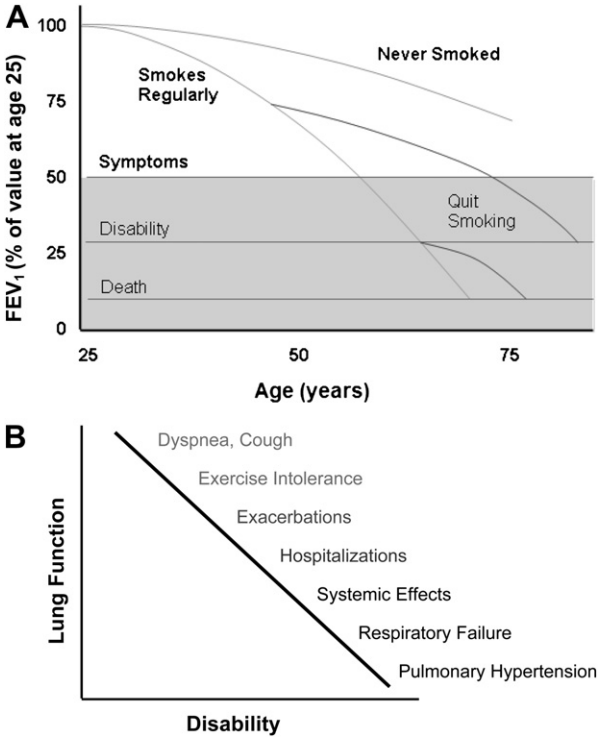

Figure 1 A: Rate of lung function decline with age in smokers and healthy individuals*. B: Natural history of COPD (*Adapted from Fletcher et al[16]) FEV1, Forced Expiratory Volume in 1 Second.

Current guidelines recommend that maintenance or regular pharmacotherapy should begin when symptomatic moderate COPD is present, with some guidelines suggesting that maintenance therapy should not be initiated until FEV_1 is <60% of predicted .[17] Treatment recommendations for mild COPD have been largely focused on symptomatic relief, with guidelines suggesting treatment should be limited to prescription of a rescue inhaler to be used on an 'as needed' basis only.[1,13,14] However, recent clinical trial results suggest there are potential benefits from regular pharmacological treatment in COPD at earlier stages of the disease. Indeed, sub-analyses of two large COPD clinical trials[18,19] suggest that treatment-related reductions in exacerbations were proportionally greater in patients with moderate COPD (GOLD stage II) compared with severe or very severe disease (GOLD stages III and IV, respectively), even though the baseline incidence of exacerbations is generally lower in earlier-disease stages.

Since patients with mild and moderate COPD comprise the largest portion of the COPD population,[10] and basic tenets of all chronic disease management programs emphasize the importance of early detection and intervention to prevent and reduce the long-term consequences of disease progression, it is essential that primary care physicians and pulmonologists further their understanding of this group of patients. This review aims to discuss the pathophysiology of mild and moderate COPD and review the evidence for benefits of maintenance therapy on lung function, exacerbation reduction, and health-related quality of life in this sub-set of COPD patients.

Pathophysiology of mild and moderate COPD

It is well recognized that COPD is caused by long-term exposure to noxious gases and particulates, especially tobacco smoke, but also wood/biomass fuel smoke, air pollution, or workplace dust or fume contaminants.[1] COPD's characteristic airflow limitation during forced expiration results predominantly from increased resistance in small airways plus increased compliance of lung tissue due to any emphysematous destruction that may be present.[20] Although lung function declines with age in all adults, even healthy non-smokers, lung function decline is accelerated in susceptible individuals who smoke cigarettes or are exposed to noxious gases and particulates (Fig. 1A, B).[16] Several long-term studies support these findings, even in patients with mild and moderate COPD.[18,19,19a]

Moderate and severe COPD is characterized by neutrophil, T-lymphocyte, and macrophage-associated inflammation of airways, lung parenchyma, and associated vasculature.[1] Histologically, progression of the disease is strongly associated with thickening of the walls of the small airways due to an increase in epithelium, lamina propria and muscle.[21] Disease progression is associated with accumulation of inflammatory mucus exudates in the airway lumen from the increase in inflammatory cells and lymphocytes organized into follicles.[21] In addition, dysfunction of the mucociliary clearance system, which normally provides secretion clearance and helps to maintain a sterile airway environment, may allow infectious agents to upregulate the adaptive immune response.[20,21,22] This, in turn, may contribute to an increase in the baseline inflammation, airflow limitation, and an increase in exacerbations. Airflow limitation and lung hyperinflation is further impacted by alveolar and elastin damage due to an imbalance of proteinases and antiproteinases, and by oxidative stress, also caused by tobacco smoke.[22,23]

Although the pathophysiology of mild COPD is less well-studied than that of later stages, patients can have considerable symptoms and pathophysiologic abnormalities even at mild levels of FEV_1 decline. Symptomatic patients with GOLD stage I disease (mild COPD) do have the above mentioned pathophysiologic changes[20] and can have significant exertional dyspnea and extensive small airway dysfunction, with their ventilatory requirements during exercise being much greater than healthy controls.[3] Importantly, patients with mild COPD, with identifiable COPD symptoms, have a significantly faster decline in FEV_1 than mild COPD patients who are completely asymptomatic or healthy persons.[24] Although the frequency of exacerbations generally increases with progressing severity of COPD, exacerbation risk is not rigidly stage-dependent. Indeed, 70% of patients with mild or moderate COPD ($FEV_1 \geq 50\%$ of the predicted) reported at least 1 exacerbation during a 1-year prospective study of COPD exacerbations.[25] Many exacerbations in COPD patients go unreported,[26] but still have significant impact on patients' health-related quality of life, and respiratory and physical functioning. COPD, whether or not diagnosed, often coexists with comorbid conditions such as cardiovascular disease, diabetes and osteoporosis, and each disease impacts the course and management of the others.[27] Therefore, even mild symptoms of dyspnea or respiratory limitations to exercise in middle-aged and elderly patients should not be disregarded as 'normal' age-related impairment, but should receive diagnostic evaluation for COPD and appropriate therapy to manage their condition.

Recommendations for treatment of mild and moderate COPD

Smoking cessation is universally recognized as essential to the treatment of COPD.[1,13,14] Recommended pharmacotherapies for COPD are applied according to symptoms and stage, beginning in mild disease with as-needed short-acting bronchodilators to relieve acute dyspnea.[1,14] Long-acting bronchodilators are recommended as maintenance therapy for moderate, severe, and very severe COPD,[1,13,14] a recommendation not always implemented by physicians and patients, even when COPD is correctly diagnosed. Indeed, a study of patients admitted to one US hospital found that only 18 of 40 patients with airway obstruction had been diagnosed with obstructive lung disease, and only 14 of these 40 were receiving bronchodilator therapy.[28] Although efforts have been made to increase awareness of COPD in the medical community over the last several years, evidence continues to suggest that changes in practice have yet to occur.[28a] Guidelines recommend adding inhaled corticosteroids (ICS) to long-acting bronchodilators for patients with frequent exacerbations and severe-to-very severe COPD[1,14]; however, ICS monotherapy is not recommended.[1] Pulmonary rehabilitation is guideline-recommended for all patients diagnosed with COPD,

regardless of disease severity, because it has been shown to significantly improve dyspnea, exercise capacity and health-related quality of life, and to reduce the number of hospitalizations.[1,13,14]

Evidence for treatment benefits in mild and moderate COPD

Early inhaled steroid studies

Although patients with mild and moderate COPD form a large part of the COPD population, most large clinical trials have assessed the safety and efficacy of COPD medications in patients with more severe COPD.[29,30] This is likely due to the fact that most clinical trials of COPD therapy are pharmaceutical studies designed to evaluate medication efficacy, with severe disease impairment providing more room to demonstrate therapeutic improvement, as required by regulatory bodies to approve new pharmacotherapies. Nevertheless, three long-term studies of ICS monotherapy in COPD included patients with mild and moderate COPD and failed to demonstrate an effect of ICS on disease progression, as assessed by rate of decline in airflow obstruction over time. The European Respiratory Society Study on Chronic Obstructive Pulmonary Disease (EUROSCOP) assessed the effect of 3 years of budesonide on mild and moderate COPD patients (entry criteria: post-bronchodilator FEV_1 50–100% of predicted, who continued to actively smoke). Budesonide increased FEV_1 versus placebo in the first 6 months of the study but had no effect on long-term decline in lung function.[31] The Lung Health Study (LHS) II assessed the effects of 3 years of triamcinolone in patients with mild-to-severe COPD (entry criteria: pre-bronchodilator FEV_1 30–90% of predicted). Triamcinolone did not slow the rate of decline in FEV_1, although it improved respiratory symptoms and decreased respiratory-related healthcare utilization.[32] The Inhaled Steroids in Obstructive Lung Disease in Europe (ISOLDE) study examined the effects of fluticasone in patients with moderate-to-severe disease (entry criteria: post-bronchodilator FEV_1 $\leq$85% of predicted). Fluticasone did not change the rate of FEV_1 decline versus placebo, but raised mean FEV_1 compared with placebo throughout the study and reduced exacerbations.[33] In addition, a *post-hoc* analysis of mild-to-moderate patients (mean post-bronchodilator FEV_1 62% of predicted) in the ISOLDE dataset showed that fluticasone did not significantly reduce the number of exacerbations in this earlier-disease population.[34] These results support guideline recommendations against the use of ICS monotherapy in any stage of COPD and for the current recommendation to add or use an ICS in combination with a long-acting bronchodilator for COPD patients.[1] Importantly, key entry criteria for these studies could have influenced their outcomes. In particular, most of these studies mandated active cigarette usage to be enrolled in the study and excluded subjects that had any airflow reversibility. As these subpopulations could behave differently from currently defined COPD patients, the results might have been different in broader populations and could explain some of the differences when compared to more recent long-term COPD studies.[35,36]

Emerging evidence for maintenance treatment of moderate COPD

Recently, published clinical trials in COPD have included patients with less severe COPD, allowing for the assessment of various COPD pharmacotherapies in patients with mild and moderate disease. Towards a Revolution in COPD Health (TORCH) was a large (>6000 patients), long-term (3 years) trial, which compared the efficacy of combined salmeterol/fluticasone with that of either component alone or placebo in moderate-to-severe COPD patients (entry criteria: pre-bronchodilator FEV_1 <60% predicted).[35] Combination treatment significantly improved post-bronchodilator FEV_1, health status, and frequency of exacerbations.[35] A *post-hoc* analysis of these data also demonstrated treatment-related reductions in the rate of FEV_1 decline.[36]

Although the primary TORCH publication did not provide analyses of patient outcomes on the basis of disease severity,[35] a recent *post-hoc* analysis of the TORCH data examined the effects of salmeterol/fluticasone combination therapy by disease stage, with an emphasis on moderate COPD.[18] Since the trial recruited patients with a pre-bronchodilator FEV_1 <60% of predicted, many patients with moderate COPD (determined by post-bronchodilator $FEV_1 \geq 50\%$ of predicted) were included in the study (>2000 patients).[18] As observed in the original study of all patients,[35] the combination treatment significantly improved post-bronchodilator FEV_1 and health status, and reduced exacerbations, compared with placebo in moderate COPD patients (Table 1). Importantly, combination treatment also reduced mortality rate in this patient population (Table 1). A reduction in the rate of FEV_1 decline in these patients narrowly missed achieving significance (Table 1).[18]

The Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) trial was another large (>6000 patients), long-term (4-years) trial assessing the impact of once-daily tiotropium versus placebo in patients who were allowed to use any additional respiratory medications except anticholinergics (other than the study drug tiotropium, if randomized to that arm).[37] Patients with moderate-to-severe disease (entry criteria: post-bronchodilator FEV_1 <70% of predicted), who were treated with tiotropium showed significant improvements in lung function, exacerbations, and quality of life. The long-term effect of tiotropium on the sub-set of patients with GOLD stage II COPD (>2500 patients) in UPLIFT was also examined in a recent *post-hoc* analysis. These results showed a significantly lower mean rate of post-bronchodilator FEV_1 decline and better health status in the tiotropium group compared with the control group (Table 1). The mean pre- and post-bronchodilator FEV_1 values were significantly higher in the tiotropium group versus the control group at all timepoints assessed during the trial. Time to first exacerbation and time to exacerbation resulting in hospitalization were also significantly longer in the tiotropium treatment group in these patients with less severe disease. In addition, risk of mortality was lower in the tiotropium group compared with the control group; however, these differences were not significant.[19]

Although the data are from *post-hoc* analysis, both of these studies suggest benefits of long-acting maintenance

Table 1 Results from TORCH and UPLIFT GOLD stage II *post-hoc* analyses.[18,19]

	TORCH Study[18]	UPLIFT Study[19]
Study interventions	Placebo, salmeterol, fluticasone, and SFC	Placebo[a], tiotropium
Population, N (n in treatment groups)	2156 (placebo 535, SFC 562)[b,c]	2739 (placebo 1384, tiotropium 1355)
Between-group difference in mean post-bronchodilator FEV_1, mL	101 (95% CI: 71, 132)[d]	Range 52−82[d]
Change in post-bronchodilator FEV_1 rate of decline, mL/year	16 (95% CI: 0, 32)	6 (95% CI: 1, 11)[d]
Change in the number of exacerbations, mean number/year	0.69 (95% CI: 0.60,0.81)[d]	0.80 (95% CI: 0.72, 0.88)[d]
SGRQ scores	−2.3(95%CI:−4.0,−0.7)[d]	Range −2.7−4.0[d]
Withdrawal during study	Placebo 35%; SFC 27%[e]	Placebo, 35%; Tiotropium 31%[d]
Hazard ratio for mortality	0.67 (95%CI: 0.45, 0.98)[d]	0.85 (95%CI: 0.66, 1.09)[f]

CI, confidence interval; FEV_1, forced expiratory volume in 1 s; SFC, salmeterol/fluticasone; SGRQ, St. George's Respiratory Questionnaire; TORCH, Towards a Revolution in COPD Health; UPLIFT, Understanding Potential Long-Term Impacts on Function with Tiotropium.
[a] Use of all respiratory medications except anticholinergics was permitted during the trial.
[b] GOLD stage II classified as $FEV_1 \geq 50\%$ of predicted.
[c] Does not include subjects who received either salmeterol or fluticasone alone.
[d] Statistically significant.
[e] Statistical significance not specified.
[f] Patients on treatment only.

therapies in the treatment of moderate COPD patients, including, reduced exacerbations, improved exercise tolerance, improved health-related quality of life and possible modification of disease progression by slowing rates of lung function decline, which could have an impact on mortality.

Emerging evidence for maintenance treatment of mild COPD

The post-hoc analysis of less severe patients from TORCH and UPLIFT, as described above, did include some subjects with mild COPD. However, the vast majority of the subjects defined as having a post-bronchodilator FEV_1 >50% predicted had moderate disease.[18,19] Thus, data from TORCH and UPLIFT may not truly represent expected results for COPD subjects with mild disease. Although the pathophysiologic observations noted earlier clearly crossd the boundaries into mild COPD, there is little clinical evidence pertaining to maintenance therapy for mild COPD subjects.There is one study specific to COPD patients with mild disease that prospectively evaluated the use of tiotropium in early disease.[38] This 12-week trial assessed the efficacy of tiotropium in 227 patients with mild and moderate COPD (entry criteria: $FEV_1 \geq 60\%$ of predicted with the study population mean post-bronchodilator FEV_1 equal to 80% of predicted). The results, as assessed by area under the curve pre-dose to 2 h post-dose for FEV_1 and FVC, as well as trough FEV_1 and trough FVC values, demonstrated that tiotropium, compared with placebo, was associated with significant improvement in airflow limitation in patients with mild and moderate COPD and that this is maintained throughout its daily dosing cycle.[38]

On the other hand, the one prospective study included a relatively small group of patients, and required that the subjects had to have some degree of dyspnea, something that all mild COPD subjects may not have. Thus, the potential benefits of long-acting maintenance medications in mild and moderate COPD should be further evaluated in additional larger-scale, prospective studies.

At this time, tiotropium and salmeterol/fluticasone combination therapy are both approved by the United States Food and Drug Administration (FDA) for maintenance treatment of airflow obstruction in COPD and to reduce COPD exacerbations.[39,40] Neither of these FDA indications has a restriction based on severity of disease, as defined by percent of predicted FEV_1 or GOLD stage. The study populations used to receive these FDA indications were somewhat different, with the salmeterol/fluticasone studies focusing on patients with severe COPD (FEV_1<50%) plus a recent history of exacerbations,[41,42] resulting in an FDA indication to reduce COPD exacerbations in patients with a history of exacerbations. The tiotropium indication was based on a broader range of COPD patients (FEV_1<60%, including the use of COPD exacerbations as a secondary endpoint from the UPLIFT trial) and did not require a history of COPD exacerbations,[37] resulting in an FDA indication that does not dictate a history of exacerbations in patients with COPD. A third medication that is a combination LABA/ICS (budesonide/formoterol) is also approved by the FDA for maintenance treatment of airflow obstruction in COPD, but currently does not include an FDA-approved indication to reduce COPD exacerbations.[43]

Conclusions

It is estimated that as many as 12 million individuals with COPD remain undiagnosed in the United States, with a large proportion of this group consisting of patients with mild and moderate COPD. In addition, many patients with a diagnosis of COPD are on no regular maintenance therapy. Smoking cessation remains a foundation of COPD management. In addition to smoking intervention, pharmacological treatment remains a key to therapy for patients with COPD. Although more data exist for COPD patients with more severe

disease, recent research suggests that the use of long-acting inhaled maintenance therapies in COPD patients with moderate disease can reduce exacerbations, improve health-related quality of life, and may slow disease progression. Early evidence also suggests the possibility that maintenance therapy might also benefit COPD patients with mild symptomatic disease. Identification and management of COPD early in its course may provide an opportunity to ameliorate its impact on patients' lives for years to come.

Conflict of interest

The author (GTF) has provided consultative services, participated in advisory boards, received research funding support and is on the speaker bureau for Boehringer Ingelheim Pharmaceuticals Inc and Pfizer Inc. This article was developed on the basis of the author's presentations and discussions at the "Long-Term Considerations in the Course and Treatment of COPD" taskforce meeting, held in Miami, Florida, Dec. 8—9, 2008. This meeting, the author's participation, and manuscript preparation were supported by Boehringer Ingelheim Pharmaceuticals, Inc (BIPI). Writing and editorial assistance was provided by Radhika Bhatia, PhD, of Envision Scientific Solutions, which was contracted by BIPI for these services. The author meets criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE), was fully responsible for all content and editorial decisions, and was involved at all stages of article development and writing. The article reflects the concepts of the author and is his sole responsibility. It was not reviewed by Boehringer Ingelheim Pharmaceuticals Inc, and Pfizer Inc, except to ensure medical and safety accuracy.

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