The role of pharmacotherapy in mild to moderate chronic obstructive pulmonary disease

Natya Raghavan, Jordan A. Guenette and Denis E. O’Donnell

Abstract: Chronic obstructive pulmonary disease (COPD) is a major health problem worldwide and most of those afflicted have mild to moderate disease as measured by spirometry. There is mounting evidence that even mild airway obstruction is associated with activity-related dyspnea, exercise limitation, impaired quality of life, increased hospitalization and mortality. As our understanding of the complex, heterogeneous pathophysiology and clinical consequences of milder COPD continues to grow, there is increasing interest in the potential impact of therapeutic interventions beyond smoking cessation. Unfortunately, few clinical trials have included patients with mild to moderate disease and the evidence base for pharmacological treatment in this subpopulation is currently lacking. Recent short-term mechanistic studies confirm that reversal of airway smooth muscle cholinergic tone consistently improves respiratory mechanics during rest and exercise in mild COPD but long-term clinical benefits remain to be evaluated. Secondary analysis of large, prospective studies designed to evaluate the efficacy of long-acting bronchodilators, inhaled corticosteroids and combination therapy indicate that patients with moderate COPD achieve comparable benefits to those with advanced disease. In the absence of evidence-based guidelines for the management of milder COPD, treatment choices are driven mainly by clinical presentation: for those with persistent and troublesome activity-related dyspnea a trial of inhaled bronchodilator therapy is justified; for those with a propensity for recurrent infective exacerbations, consideration of additional anti-inflammatory treatment seems reasonable. In this paper, we review the current knowledge base and emerging paradigm for the pharmacological treatment of mild to moderate COPD.

Keywords: bronchodilators, chronic obstructive pulmonary disease, dyspnea, exacerbations, Global Initiative for Chronic Obstructive Lung Disease stage I, inhaled corticosteroids

Introduction

Chronic obstructive pulmonary disease (COPD) is a major health problem worldwide. The majority of those afflicted have milder disease which often goes undiagnosed and untreated [Rabe et al. 2007]. Even mild to moderate disease has been associated with an accelerated decline in lung function, impaired quality of life, increased health care utilization and increased mortality [de Marco et al. 2009; Benfield et al. 2008]. Although many advances have been made in the treatment of this debilitating illness over the past few years, only a handful of randomized clinical trials include patients with mild disease. As disease awareness increases and targeted screening efforts become more widespread, it is anticipated that an increasing number of smokers will be diagnosed earlier in the course of their disease. It is therefore imperative that we better understand the pathophysiology and pharmacological treatment options for mild disease.

The definition of COPD as per the Global Initiative for Chronic Obstructive Lung Disease (GOLD) is a fixed ratio of forced expiratory volume in 1 s to forced vital capacity (FEV1/FVC) of less than 0.70. Severity is then graded based on postbronchodilator FEV1 with mild disease (stage I) FEV1 ≥80% predicted and moderate (stage II) 50–80% predicted [Rabe et al. 2007]. Studies have indicated that the use of the fixed ratio for diagnosis of COPD may lead
to underestimation of the disease in younger patients and false positives in older patients [Schermer et al. 2008; James et al. 2007]. The use of the lower limit of normal for the ratio of FEV1/FVC as derived from predictive equations may be more accurate; however its use is still not well established [Miller et al. 2005]. As there are only limited data on pharmacological interventions in stage I COPD, we will cover the current evidence base for the treatment of both stage I and II COPD as defined by the GOLD criteria.

The group comprising ‘milder’ COPD (stages I and II) is known to be both pathophysiologically and clinically heterogeneous with highly variable rates of progression. It appears that those with respiratory symptoms tend to have more accelerated progression of airflow obstruction while those who are asymptomatic are less likely to have progressive disease [de Marco et al. 2009; Bridevaux et al. 2008]. We must therefore examine the current evidence base for this heterogeneous group with a critical eye because there may be some in this group who never develop worsening airflow obstruction or troublesome respiratory symptoms and should therefore be spared long-term pharmacotherapy with agents that have known side effects.

Is there a rationale for earlier treatment in COPD?

Despite relatively preserved spirometry, milder COPD has been associated with profound pathological and physiological changes at the level of the small airways (<2 mm). Hogg and colleagues have demonstrated the presence of active inflammation of the small airways in patients with mild to moderate disease [Hogg et al. 2004]. These pathological changes have also been associated with abnormalities in tests of small airway function such as the nitrogen washout [Stanescu et al. 1998] as well as significant ventilation to perfusion mismatch and an increased alveolar arterial oxygen gradient [Rodriguez-Roisin et al. 2009; Barbera et al. 1990]. Abnormalities can also be visualized radiographically where increased airway wall thickness, emphysema and lung over-inflation are seen even in the mildest stages of disease [Yuan et al. 2009; Gelb et al. 1996; Kuwano et al. 1990]. New data are also emerging on the presence of resting lung hyperinflation in mild disease including an increase in residual volume, functional residual capacity and specific airways resistance in GOLD stage I disease [Deesomchok et al. 2010].

The presence of extensive airway and parenchymal abnormalities has also been shown to correlate with troublesome symptoms. Indeed, symptomatic patients with stage I disease have reduced exercise performance, as well as an increase in dyspnea intensity, ventilatory requirements, and dynamic hyperinflation during cycle exercise compared with healthy controls [Ofir et al. 2008]. There is also evidence for a decline in physical activity across all stages of COPD compared with normal controls [Garcia-Aymerich et al. 2009; Watz et al. 2009, 2008]. Thus it appears that the pathophysiological changes seen in mild COPD contribute to activity related dyspnea. It is likely that such patients begin to curtail their activities to avoid discomfort. It is therefore reasonable to consider treatment in symptomatic patients with mild COPD in an effort to improve their respiratory symptoms, quality of life, functional status, and ideally, to halt the natural progression of this disease.

Therapeutic interventions

Smoking cessation

The first priority in all stages of COPD and especially in mild to moderate disease is halting the decline in lung function and the progression of respiratory symptoms. Smoking cessation is the only intervention proven to improve lung function and alter the course of disease in COPD [Anthonisen et al. 2002; Fletcher and Peto, 1977]. The Lung Health Study was designed to evaluate the effect of a 10-week smoking cessation intervention alone and in addition to inhaled ipratropium bromide versus usual care in mild to moderate COPD. Average FEV1 was 75% predicted. The smoking intervention consisted of meeting in groups with a health educator for 12 visits over 10 weeks and also the provision of nicotine replacement therapy at no cost. Those receiving the smoking cessation intervention had significantly higher sustained quit rates of 22% at 5 years versus 5% in the group receiving usual care. Smoking cessation was associated with a smaller decline in FEV1 over the course of the study as well as a decrease in respiratory symptoms [Kanner et al. 1999; Anthonisen et al. 1994]. A follow up of this cohort at 14.5 years demonstrated significant all-cause mortality benefit, with those in the usual care group having a hazard ratio of 1.18 over the smoking intervention group [Anthonisen et al. 2005].
A number of pharmacological agents are available to aid in smoking cessation and have been shown to improve quit rates in those with and without COPD when compared with placebo. These options include nicotine replacement in various forms (patch, gum, inhaler, nasal spray, lozenge), bupropion, nortriptyline and varenicline [Jorenby et al. 2006; Tashkin et al. 2001]. Both nicotine replacement and the antidepressant agents, bupropion and nortriptyline have been studied in those with mild to moderate COPD, however varenicline has only been tested in the general smoking population [Tashkin and Murray, 2009]. In the general smoking population, response rates are similar regardless of the type of nicotine replacement. The most commonly used preparation is the patch which comes in 7, 14 and 21 mg/24 h doses which are quite well tolerated. Bupropion is recommended at a dose of 150 mg twice daily to be taken orally and should be started prior to smoking cessation. The most common side effect is insomnia. The most serious side effect is lowering of the seizure threshold and thus the drug is contraindicated in those with a history of seizures [Tashkin et al. 2001]. Both nicotine replacement and bupropion approximately double quit rates when compared with placebo and have been used together successfully [Tashkin and Murray, 2009]. Varenicline, an \( \alpha_2 \beta_4 \) nicotinic acetylcholine receptor agonist, works by both reducing cravings as well as blocking the positive reinforcement of smoking through partial antagonist effect. In a general population of smokers it has been shown to approximately triple quit rates when compared with placebo and is more effective in the short term than bupropion. It is titrated to a dose of 1 mg twice daily and should be started 7 days prior to smoking cessation. Side effects include nausea and this medication must be used with caution in those with mood disorders because of an increased risk of suicidal ideation [Jorenby et al. 2006].

### Nonpharmacological interventions

Patients with COPD require comprehensive care and the role of nonpharmacological interventions must be stressed (Table 1) [O’Donnell et al. 2007]. Promotion of regular physical activity should be a consistent message to all patients with COPD. Although data on respiratory rehabilitation in mild disease are limited, studies including those with moderate disease have demonstrated consistent benefits in terms of improved exercise tolerance and quality of life [Rossi et al. 2005; Clark et al. 2000; Berry et al. 1999]. In addition, studies have shown that smokers without airflow obstruction who are physically active have a decreased rate of decline in FEV\(_1\) and decreased incidence of COPD compared with those who are more sedentary [Garcia-Aymerich et al. 2009]. There is evidence for increased lower respiratory tract infections in mild to moderate COPD and thus it is reasonable to consider immunization against influenza and pneumococcus. Annual influenza vaccination is recommended based on extrapolation from studies showing a benefit to both morbidity and mortality in elderly patients with chronic lung disease [Nichol et al. 1999]. The American Thoracic Society currently recommends both influenza and pneumococcal vaccines in all smokers, but there are few data to support routine pneumococcal immunization in ex-smokers with mild COPD [Mandell et al. 2007].

### Pharmacological interventions

**Short-acting bronchodilators.** In the Lung Health Study described above inhaled ipratropium bromide at a dose of two inhalations three times a day was associated with a small average improvement in FEV\(_1\) of 40 ml in the first year of the study but subsequently provided no difference in decline of lung function when compared with placebo. The beneficial effect was lost after withdrawal of the medication [Anthonisen et al. 1994]. Nevertheless, this first examination into the use of a short-acting bronchodilator in mild to moderate disease did demonstrate some short-term benefit.

---

**Table 1. Management of symptomatic milder chronic obstructive pulmonary disease.**

<table>
<thead>
<tr>
<th>Education and smoking cessation programs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention of exacerbations (vaccinations)</td>
</tr>
<tr>
<td>Initiation of bronchodilator therapy</td>
</tr>
<tr>
<td>Encouragement of regular physical activity</td>
</tr>
<tr>
<td>Close follow up and disease monitoring</td>
</tr>
</tbody>
</table>

[Adapted with permission from O’Donnell et al. (2007).]
In order to examine the mechanisms of relief following the administration of a short-acting bronchodilator, a small, mechanistic, placebo-controlled, proof-of-concept study was undertaken by O’Donnell and colleagues in symptomatic GOLD stage I COPD [O’Donnell et al. 2009]. They demonstrated that cholinergic tone of airway smooth muscle (which was partially reversible) contributed to abnormalities of dynamic respiratory mechanics during exercise in these patients. Patients were randomized to either a single dose (500 μg) of inhaled ipratropium bromide or placebo prior to undergoing constant-load exercise at 80–85% of maximal work rate. These patients had mild resting hyperinflation with mean total lung capacity and residual volume greater than 120% predicted. Treatment with inhaled ipratropium bromide was associated with a small but consistent improvement in FEV\textsubscript{1}, airways resistance, and residual volume at rest. During exercise, there was a significant reduction in pulmonary resistance, dynamic lung hyperinflation and work of breathing, and an increase in tidal volume expansion (Figure 1). The reduction in lung hyperinflation was also associated with decreased dyspnea intensity for the same ventilation after treatment with ipratropium bromide compared with placebo [O’Donnell et al. 2009]. In this study, symptomatic patients with mild COPD derived benefit from short-acting anticholinergic agents, thus providing a sound basis for the use of these agents in those patients with mild COPD who have exercise-induced dyspnea. Similar results were found in a retrospective review of static lung volumes after inhalation of a short-acting β\textsubscript{2}-agonist (salbutamol) by Deesomchok and colleagues [Deesomchok et al. 2010]. There was a consistent improvement in residual volume after inhalation of 200 μg of salbutamol across all stages of disease from GOLD I to IV as shown in Figure 2 [Deesomchok et al. 2010]

Long-acting bronchodilators. Tiotropium is a long-acting inhaled anticholinergic which has established efficacy in moderate to severe COPD. Concern has been raised over extrapolating these results to those with milder disease, especially since this may portend prolonged treatment over many decades. A study by Johansson and colleagues looked specifically at mild to moderate disease and included those with an FEV\textsubscript{1} greater than 60% predicted (mean post-bronchodilator FEV\textsubscript{1} 80% predicted) who were symptomatic [Johansson et al. 2008]. They found a small but statistically significant improvement in prebronchodilator FEV\textsubscript{1} by an average of 74 ml at day 85 compared with baseline. In addition, there was a significant, albeit small, improvement in the change in both FEV\textsubscript{1} and FVC postbronchodilator throughout the study of 157 ml and 187 ml, respectively. These changes were not associated with an improvement in dyspnea (measured by the Baseline Dyspnea Index and Medical Research Council dyspnea scales) or in quality of life [Johansson et al. 2008]. This may be because of the lack of sensitivity of these questionnaires in milder disease or the relatively minor symptoms experienced by these patients at baseline.

The Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) was a randomized, double-blind, placebo-controlled multicentre trial that established the efficacy and safety of tiotropium in advanced COPD. In a prespecified subgroup secondary analysis that looked specifically at stage II disease, 2739 patients were randomized to tiotropium versus placebo. Mean postbronchodilator FEV\textsubscript{1} was 59% predicted in this subgroup. There was a small difference in the rate of decline in FEV\textsubscript{1} per year in those receiving tiotropium versus those receiving placebo of 6 ml/year. Although this may reflect disease modification, the longer-term clinical consequence of this modest improvement is unclear [Decramer et al. 2009]. As seen in the study by Johansson and colleagues, there was a significant improvement in both pre- and postbronchodilator FEV\textsubscript{1} and FVC in those receiving tiotropium [Johansson et al. 2008]. Health status as measured by the St George’s Respiratory Questionnaire was improved in the treatment group over the first 6 months but thereafter declined at a similar rate to those receiving placebo. Time to first exacerbation and to exacerbation requiring hospitalization were both significantly prolonged in patients receiving tiotropium. It must be noted that participants were allowed to continue their inhaled corticosteroid (ICS), long-acting β\textsubscript{2}-agonist or the combination and thus it is difficult to separate the effects of tiotropium from those of the other agents [Decramer et al. 2009]. It is also noteworthy that this group represents a more severe subset of those with GOLD stage II disease and thus care must be taken in extrapolating these results to all patients with mild to moderate disease. The use of tiotropium has been associated with dry mouth and urinary retention and must be used with
Figure 1. Ventilatory responses to constant-load cycle testing against exercise time after ipratropium bromide compared with placebo in 16 patients with mild chronic obstructive pulmonary disease. Tidal volume (VT) and inspiratory capacity were greater, and estimates of expiratory flow limitation (EFL) were lower after ipratropium bromide than after placebo; minute ventilation, breathing frequency (F) and inspiratory reserve volume were not different between treatments. TLC, total lung capacity. *p < 0.05 ipratropium bromide versus placebo at a given time point or at peak exercise. Values are mean (SEM). Adapted with permission from O’Donnell and colleagues [O’Donnell et al. 2009].
caution in those with glaucoma, bladder neck obstruction or prostatic hypertrophy [Kesten et al. 2006].

Any benefits of inhaled bronchodilator treatment in mild to moderate disease must be carefully weighed against any potential harm in view of the limited safety data from clinical trials in this subgroup [Enright, 2009]. Given the sound physiological basis for symptomatic benefit, it seems reasonable to offer patients with persistent activity-related dyspnea a trial of bronchodilator treatment on an individual basis.

Inhaled corticosteroids. As airway inflammation is the pivotal abnormality of COPD, regardless of severity category, it is not surprising that ICS were among the first agents to be tested in an attempt to modify the natural history of COPD. In 1999, the European Respiratory Society Study on Chronic Obstructive Pulmonary Disease (EUROSCOP) examined the effects of inhaled budesonide (400 μg) twice daily versus placebo in 1277 patients with mild to moderate disease (mean prebronchodilator FEV₁ 77% predicted) who continued to smoke. They found that treatment was associated with a small increase in FEV₁ over the first 6 months at a rate of 17 ml/year. However, subsequent decline in lung function was the same as in those receiving placebo. The group receiving budesonide also demonstrated increased skin bruising, an indication of important systemic exposure. Additional side effects included oropharyngeal candidiasis, local irritation of the throat and dysphonia [Pauwels et al. 1999]. A similar trial by Vestbo and colleagues that included all participants of the Copenhagen City Heart Study who had airflow obstruction (on spirometry) investigated the impact of 3 years of inhaled budesonide (800 μg and 400 μg for 6 months followed by 400 μg twice daily) versus placebo in 290 patients with milder disease (mean postbronchodilator FEV₁ 87% predicted) [Vestbo et al. 1999]. They also found no difference in the rate of decline in FEV₁ between the two groups over the course of the study [Vestbo et al. 1999]. However, this study was likely underpowered to detect differences in this primary outcome variable.

Concomitant ischemic heart disease has been established as a major cause of death in patients with COPD. Lofdahl and colleagues undertook a retrospective analysis of the EUROSCOP cohort (prebronchodilator FEV₁ 77% predicted) comparing the effect of inhaled budesonide versus placebo on the reported incidence of angina, myocardial infarction, coronary artery disease and myocardial ischemia (ischemic cardiac event rate) [Lofdahl et al. 2007]. The treatment group had a ratio of ischemic cardiac events of 0.58 when compared with the placebo group. There was a reduction in both the number of patients who experienced an event as well as the total number of events in the group receiving budesonide [Lofdahl et al. 2007]. Although of interest, the generalizability of this result from a retrospective chart review is limited.

ICS therapy has been shown to reduce the frequency and severity of exacerbations in patients with COPD with moderate to severe airway obstruction. In 2003 Jones and colleagues evaluated the use of fluticasone 500 μg twice daily versus placebo on the rate of exacerbation over...
3 years. They found no difference in the rate of exacerbation in those with mild to moderate disease (FEV$_1$ > 50%), although there was a significantly lower rate of exacerbation in the treatment group for those with severe disease [Jones et al. 2003].

Despite the poor evidence for inhaled steroids in early disease, many patients receive the treatment. The majority are those cared for in the primary care setting where repeated studies have demonstrated inadequate access to spirometry [Calverley and Bellamy, 2000]. This led Choudhury and colleagues to investigate the impact of withdrawal of ICS in the primary care setting in 260 patients who had moderate or severe disease (average postbronchodilator FEV$_1$ 54%) [Choudhury et al. 2007]. This study had a large proportion of patients break protocol and return to their baseline ICS. However, when analyzed per protocol, it was found that those receiving placebo had an elevated relative risk of suffering an exacerbation when compared with randomized to receive fluticasone 500 µg twice daily. The analysis was performed separately in those with moderate disease (FEV$_1$ > 50% with up to one exacerbation/year) than those with more severe disease who met recommendations for prescription of ICS in COPD and the finding was similar in both groups. In a recent study, investigators proposed that a distinct ‘exacerbation’ phenotype exists in COPD and that this manifests in patients with GOLD stage II COPD, 39% of whom experience at least one exacerbation per year [Hurst et al. 2010]. It seems reasonable that such patients with moderate COPD who are prone to exacerbations be identified for possible ICS therapy. Currently, however, no evidence-based guidelines exist regarding the appropriate use of ICS in patients with COPD who fit GOLD stage I and milder GOLD stage II criteria.

**Combination of long-acting bronchodilator and inhaled corticosteroid.** Finally the use of the combination of a long-acting inhaled β$_2$-agonist and ICS has gained popularity in the treatment of patients with COPD with advanced disease and frequent exacerbations. A recent retrospective analysis was undertaken of the multinational TORCH trial by Jenkins and colleagues [Jenkins et al. 2009] whereby the benefit was analyzed by stage of COPD. The group classified as stage II also included a few patients with stage I disease; however, the overall severity was quite advanced with a mean postbronchodilator FEV$_1$ of 59%. The combination of salmeterol and fluticasone in a single inhaler was found to be associated with an improvement in lung function (mean increase in FEV$_1$ of 101 ml), decreased exacerbation rates, improved quality of life and a decrease in mortality. The magnitude of these benefits was small but broadly similar to the effects seen in the group as a whole. The mortality benefit did not reach statistical significance in the primary analysis, therefore this finding in a retrospective post-hoc subgroup analysis must be interpreted with caution. The effect on all of the measured outcomes was consistently greater for the fluticasone/salmeterol combination compared with fluticasone alone. Thus, the role of ICS monotherapy in COPD of any severity appears to be poorly supported. Again, care must be taken in generalizing these results to those with milder disease. The side effects reported in this subgroup analysis were similar to those of the group as a whole, with an increased risk of pneumonia in those receiving ICS (either monotherapy or combination). An increased incidence of oropharyngeal candidiasis and dysphonia were also seen in the groups receiving ICS.

**Phosphodieseterase 4 inhibitors.** The search for novel nonsteroidal anti-inflammatory agents has led to the development of roflumilast, a targeted inhibitor of phosphodieseterase 4 that is given orally once a day. To date, the data in moderate to severe COPD (average postbronchodilator FEV$_1$ of around 55%) indicate improvement in lung function even when added to salmeterol or tiotropium in patients with a chronic bronchitis phenotype who were prone to exacerbations. After a 24-week period prebronchodilator FEV$_1$ improved by 49 ml in the salmeterol plus roflumilast group and 80 ml in the tiotropium plus roflumilast group *versus* the long-acting bronchodilator and placebo groups [Fabbri et al. 2009]. The generalizability of these results to all patients with GOLD stage II COPD is currently unknown and long-term safety data are still lacking to support its routine use in this population. No trials have examined its effect on mild COPD.

**Conclusions**

In summary, the longstanding view that milder airway obstruction has few clinical consequences and requires no therapeutic intervention is probably erroneous. We now know that even patients with mild COPD have heterogeneous pathophysiological abnormalities that in many cases are
associated with objective morbidity. The paucity of data and the lack of evidence-based guidelines for the pharmacological management in GOLD stage I disease (or indeed in COPD populations with FEV₁ > 65% predicted) means that the caregiver must exercise best clinical judgment on an individual patient basis. Smoking cessation, as the only intervention proven to modify disease progression, must be emphasized as a pivotal management intervention for all stages of COPD. It seems reasonable to offer treatment with regular inhaled bronchodilators to patients with mild spirometric abnormalities with persistent activity-related dyspnea. There is currently inadequate information to guide clinicians as to the optimal timing to transition from as needed short-acting bronchodilators to regular long-acting bronchodilator therapy. For patients with moderate COPD, there is increasing evidence (albeit from retrospective analyses) that long-acting bronchodilators such as tiotropium are effective in achieving sustained bronchodilatation, improved perceived health status and reduced exacerbations. The role of monotherapy with an ICS in patients with mild to moderate COPD (who are prone to exacerbations) is no longer tenable based on lack of proven efficacy as well as inferiority to a single inhaler combination of an ICS and a long-acting β₂-agonist (LABA). An ICS-/LABA combination appears equally effective in GOLD stage II disease compared with more advanced GOLD stages in improving lung function, quality of life and exacerbation rates. The caveat remains that subgroups of the recent clinical trials included in secondary analyses were closer to GOLD stage III in severity. Finally, although newer phosphodiesterase 4 inhibitors hold some promise and biological plausibility as anti-inflammatory agents, their efficacy in patients with mild to moderate COPD has yet to be formally evaluated. Clearly, appropriately designed prospective trials of bronchodilator efficacy are required in milder COPD to guide best clinical management.

**Conflict of interest statement**

N. Raghavan and J.A. Guenette do not have any conflicts of interest to report. D.E. O'Donnell has served on advisory boards for Boehringer Ingelheim, Pfizer, GSK and Roche; has received speaker fees from Boehringer Ingelheim, Pfizer and GSK; and has received industry-sponsored grants from AstraZeneca, Boehringer Ingelheim, GSK, Merck Frost Canada, Novartis and Pfizer.

**References**


Clark, C.J., Cochrane, L.M., Mackay, E. and Paton, B. (2000) Skeletal muscle strength and endurance in...


http://tar.sagepub.com

N Raghavan, JA Guenette et al.


