It's about time — directing our attention toward modifying the course of COPD

Mario Cazzola¹, Nicola A. Hanania²,*, Paul W Jones³, Donald A. Mahler⁴, Barry Make⁵, Jill Ohar⁶ and Stephen Rennard⁶

¹ University of Rome Tor Vergata, Department of Internal Medicine, Unit of Respiratory Diseases, Rome, Italy
² Baylor College of Medicine, Division of Pulmonary and Critical Care Medicine, Houston, TX, USA
³ Division of Cardiac and Vascular Science, St. Georges, University of London, London, UK
⁴ Section of Pulmonary & Critical Medicine, Dartmouth-Hitchcock Medical Center, One Medical Center Drive, Lebanon, NH, USA
⁵ Department of Medicine, National Jewish Medical and Research Centre, Denver, CO, USA
⁶ Department of Internal Medicine, Section on Pulmonary, Critical Care, Allergy and Immunologic Diseases, Wake Forest University School of Medicine, Winston Salem, NC, USA
⁷ Department of Internal Medicine, University of Nebraska Medical Centre, Omaha, NE, USA

KEYWORDS
Chronic obstructive pulmonary disease; Bronchodilators; Smoking cessation; Therapy; Inhaled corticosteroids; Outcomes; Formoterol; Salmeterol; Tiotropium;

Summary The course of COPD has traditionally been equated with an accelerated decline in the forced expiratory volume in one second (FEV₁) over time in patients with COPD, compared to healthy individuals. However, other important clinical outcomes associated with COPD also worsen over time and should also be considered in conceptualizing the course of COPD. These include health status, breathlessness related to activities of daily living, exercise capacity, the frequency of exacerbations, and peripheral muscle weakness. These outcomes are often quite responsive to therapy of COPD. Presently there is no evidence that any treatment other than smoking cessation can normalise the rate of decline of FEV₁, and therefore be considered as modifying the physiologic course of the disease. Thus, smoking cessation reigns as the primary disease modifying strategy in COPD. Even though there are a number of smoking cessation products on the market and smoking prevalence continues to decrease marginally each year, more needs to be done to provide comprehensive programmes to help people quit smoking. In the US in 2004, 37.5% of preventable deaths were found to be tobacco-related.

The FEV₁ does not reflect the clinical manifestations or the total burden of this multidimensional illness. As novel therapeutic agents become available that may alter the underlying pathology of COPD, additional markers and outcomes of
disease progression will be needed to provide a more comprehensive assessment. There has been increasing interest in predicting and assessing mortality as it is the final outcome of disease progression. In this review we have considered three approaches toward modifying the course of COPD: smoking cessation, reduction in lung hyperinflation through medical and surgical approaches, and long-term pharmacotherapy.

© 2008 Elsevier Ltd. All rights reserved.

Smoking cessation

Demographics – the need

Presently, smoking cessation is the only intervention shown to modify the physiologic course of COPD1,2. There are 46 million smokers in the US and according to the Department of Health and Human Services, 1/3 of all tobacco users in that country will die prematurely of tobacco-related disease3. In a study published in 2004, 18% of total deaths in the United States and 37.5% of preventable deaths in the U.S. were found to be tobacco-related3. Since the publication of the first surgeon general’s report that linked tobacco use to illness and death, cigarette smoking has continuously declined in the US. Seventy percent of current smokers want to quit4,5 and 80% have made at least one quit attempt in their life6. Thirty five percent of smokers initiate a quit attempt each year4–6 but despite the market availability currently of seven effective smoking cessation products representing three different drug classes, only 2.5%5 are successful. Clearly there is more work to be done.

Our previous failures

Nicotine polacrilex gum was introduced into the market place as pharmacotherapy for cigarette addiction 30 years ago7. Since that time, five other nicotine replacement treatment (NRT) products and bupropion (Zyban®) have come into the market place. Each of these products had at the time of launch into the market and continues to have statistically significant and clinically relevant efficacy. Smoking cessation pharmacotherapies have enjoyed instant and impressive gains in market share soon after launch followed by precipitous declines in sales despite their demonstrated efficacy. Something is missing in the use or marketing of nicotine addiction pharmacotherapies.

Hope for new products like varenicline

Varenicline is an 4β2 nicotine acetylcholine receptor partial agonist introduced into the market in 2006. Results of two randomized, double blind placebo and active treatment controlled studies5,9 revealed impressive quit rates of 21.9 and 23.0% at 12 months (Figure 1). In these two studies varenicline had nearly significant (p = 0.057) and significantly (p = 0.004) greater abstinence rates than its active comparator, bupropion. While varenicline is an exciting new addition to our arsenal of smoking cessation pharmacotherapies it is not without warts and blemishes10.

Success of FDNY (New York Fire Department)

In 2006, a study was published entitled “Tobacco Free with FDNY”11. In this study a highly motivated population, FDNY members and their families, were offered bupropion and nicotine replacement products (patch, inhaler and nasal spray) in conjunction with counseling for 3 months, free of charge. Drug dosing was based on pretreatment cigarette consumption and adjusted based on withdrawal symptoms and adverse events. Captured data included pretreatment Fagerstrom score and biochemical or family member confirmed abstinence at 3, 6, and 12 months. A remarkable 37% of participants were smoke free at 12 months11. Enrollees required on average a greater number of additional pharmacotherapies and dose of nicotine than predicted by pretreatment cigarette consumption (Table 1). Treatment efficacy was directly proportional to pretreatment cigarette consumption, a finding that is diametrically opposite to previously published studies of nicotine pharmacotherapies7. Abstinence rates correlated inversely with tobacco dependency as measured by the Fagerstrom score.

Other attempts at individualised therapy

Another study evaluated the efficacy of bupropion treatment lasting 52 weeks12. Participants were treated with open label bupropion for 7 weeks followed by randomisation of all abstinent subjects to an additional 45 weeks of bupropion or placebo and followed for an additional 52 weeks after cessation of treatment. The point prevalence of smoking abstinence was significantly higher in the extended bupropion treatment group than the placebo group.
Modifying the course of COPD

Figure 1  Abstinence rates in 2 studies were significantly greater for varenicline vs. placebo at 1 year. In one of the two studies varenicline was better than bupropion.1 Gonzales D et al. JAMA. 2006;296:47–55; 2 Jorenby DE et al. JAMA. 2006;296:56–63.

Table 1 “Tobacco Free With FDNY” Medication protocol with proposed treatment assignments based on protocol (tobacco use alone) vs. actual regimen

<table>
<thead>
<tr>
<th>Cigarettes smoked per day on study entry, average no.</th>
<th>Daily medication regimen</th>
<th>Enrollees</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Based on protocol alone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n (%)</td>
</tr>
<tr>
<td>1−5</td>
<td>Inhaler as needed (0−6 cartridges)</td>
<td>11 (5)</td>
</tr>
<tr>
<td>6−19</td>
<td>Inhaler as needed (0−6 cartridges) or patch (15 mg) while awake</td>
<td>34 (15)</td>
</tr>
<tr>
<td>20−30</td>
<td>Inhaler as needed (0−12 cartridges) and patch (15 mg) while awake</td>
<td>111 (50)</td>
</tr>
<tr>
<td>31−40</td>
<td>Inhaler as needed (0−12 cartridges) and patch (30 mg; two patches) while awake</td>
<td>52 (24)</td>
</tr>
<tr>
<td>&gt;40</td>
<td>Inhaler as needed (0−12 cartridges) and patch (30 mg; two patches) and spray prn for immediate relief</td>
<td>12 (5)</td>
</tr>
<tr>
<td>Severe tobacco cessation anxiety</td>
<td>Add bupropion SR (150 mg bid) to any of the above regimens</td>
<td>30 (14)</td>
</tr>
</tbody>
</table>

(55.1 vs 42.3%; p = 0.008) at the end of treatment (52 weeks). Abstinence declined over time for both groups (47.7 vs 37.7%, respectively at week 78; p = 0.034). At one year post active therapy the difference between the bupropion treated and placebo groups was lost (abstinence of 41.6 and 40.0%, respectively at week 104).

A similar design was utilised by Tonstad and colleagues when evaluating the safety and efficacy of extended use varenicline13. Continuous abstinence rates for weeks 13–52 were 43.6 and 36.9%, respectively (p = 0.02). Continued follow up of this cohort will provide information on the role of extended therapy varenicline.

Need for creative approaches

The studies evaluating extended therapy with bupropion and varenicline show that success rates approaching 40% can be achieved12,13. These studies also highlight the importance of individualized pharmacotherapy and coexistent prolonged counseling. The new varenicline (Chantix®) smoking cessation program combines pharmacotherapy with online interactive computer-based behavioral counseling. Much has been written on this subject but little that is published has long term cessation rates. Etter and coworkers demonstrated a 2.6 fold increased abstinence rate (5.8% vs 2.2%; p < 0.001) at
7 months after entry into program using computer generated personalised letters\textsuperscript{14}. The advantage of the intervention was lost at 24 months follow-up\textsuperscript{15}.

Stretcher and colleagues evaluated the efficacy web-based tailored vs. web-based non-tailored behavioral support in conjunction with nicotine patches. Continuous abstinence at 12 weeks was 22.8 vs 18.1\% for tailored and non-tailored support (p = 0.0006), respectively\textsuperscript{16} but no long term data is yet published in this cohort.

The expense of web-based tailored behavioral support is primarily in the set up of the system and extended duration of use would add little to the cost. If this modality proves efficacious and the abstinence rates of long term face to face therapy is translatable to this system perhaps lasting cessation could be achieved on greater numbers of smokers at a lesser cost.

Use of pharmacotherapy is not enough

Cigarette smoking prevalence dropped dramatically after the publication of the first surgeons general’s report on smoking and health (Figure 2). Since that time prevalence rates have continued to decrease every year. Recently these changes have been marginal\textsuperscript{17} and nearly 21\% of Americans still smoke. In a recent editorial\textsuperscript{18}, 5 basic ways to help smokers quit were listed. Providing cessation aids such as NRT, bupropion and varenicline used in conjunction with behavioral therapy was just one of these five. The others were; 1) increase the price of a pack of cigarettes, 2) ban smoking in public places, 3) disseminate effective counter-marketing messages about smoking and 4) ban tobacco advertising. State and local governments must work with healthcare workers and insurers to provide a comprehensive programme that includes all of the above if smoking prevalence is to drop precipitously.

**Modifying the course of COPD with medical and surgical lung volume reduction surgery**

There has been increasing interest in predicting and assessing mortality, as it can be considered the final outcome of disease progression. Accordingly, international guidelines have included “reducing mortality” as one of the goals of treatment of COPD\textsuperscript{19–21}. The following discussion deals with how medical and surgical lung volume reduction might prolong survival.

**Hyperinflation in COPD**

Lung hyperinflation, manifested by an increased lung volume at the end of expiration and an increased residual volume, is usually present in COPD patients when they are at rest, but is commonly increased when they exercise. While a decreased elastic recoil pressure is important as a cause of resting hyperinflation, it has become clear that in many patients with COPD, end-expiratory lung volumes are also dynamically set. Based on the results of five studies, approximately 48\% of patients with stable COPD have expiratory flow limitation (EFL) during tidal breathing at rest\textsuperscript{22}. As a result of EFL, patients breathe at higher lung volumes (i.e., they have lung hyperinflation). Breathing at higher volumes permits expiratory flow to be increased and reduces the resistive work of breathing, but this is at the cost of a substantially increased elastic work of breathing. A reduced inspiratory capacity (IC), which is the maximal volume of air that can be inhaled from the end of tidal breath, reflects an elevation in ELV, or functional residual capacity (FRC).

O’Donnell and colleagues\textsuperscript{23} reported that 80\% of 105 patients who had severe COPD (FEV\textsubscript{1} = 37 ± 13\% predicted), resting hyperinflation (FRC = 174 ± 43\% predicted), and a reduced diffusing capacity (57 ± 21\% predicted) exhibited dynamic hyperinflation during cycle ergometry as defined by a decrease in IC outside of 95\% confidence limits. However, the prevalence of dynamic hyperinflation is unknown in patients with moderate airflow obstruction.

Hyperinflation causes shortening of the vertical muscle fibers of the diaphragm, the development of intrinsic positive end-expiratory pressure, and a mechanical restriction with reduced tidal volume\textsuperscript{23}. These alterations have a deleterious effect on the mechanics of breathing and contribute to breathlessness. With the increased respiratory rate that occurs with exercise patients with COPD may develop EFL and be unable to exhale completely. As a result, they experience an increase in end-expiratory lung volume. This development of dy-

![Figure 2](smoking-prevalence.png) **Figure 2** Smoking prevalence in 2004 was 20.1\% but has changed only 4.6\% since 1995.
Figure 3  Proposed mechanisms whereby medical and surgical lung volume reduction treatments might increase survival in patients with chronic obstructive pulmonary disease.

Dynamic hyperinflation can be demonstrated by a reduction in IC as TLC remains constant.

Based on the pathophysiologic mechanisms described above, it is expected that medical and surgical interventions which reduce lung volumes (and thereby reduce dyspnea) might also increase survival in patients with COPD. The rationale for this speculation is:

a. A decreased inspiratory capacity / total lung capacity (IC/TLC) ratio and an increased residual volume (RV) predict mortality in patients with COPD; thus hyperinflation is related to mortality in this disease.

b. Some COPD therapies can increase the IC or decrease the RV, indicating they have a lung volume reduction effect.

c. Since hyperinflation predicts mortality independent of airflow limitation, interventions that deflate the hyperinflated lung (as measured by an increase in the IC/TLC and/or a decrease in RV) very possibly will prolong survival (Figure 3).

Theoretical support for this hypothesis is available from both animal and human studies. Excessive stretch of the lung has been shown to promote inflammation and release of cytokines in animal models. Moreover, strenuous resistive breathing induces release of pro-inflammatory cytokines. In patients with adult respiratory distress syndrome (ARDS) mechanical ventilation with lower tidal volumes (6 ml/kg) (i.e., less inflation of the lung parenchyma) has been shown to decrease mortality compared with use of traditional tidal volumes (12 ml/kg)24.

Medical volume reduction

Four different medical interventions have been shown to reduce lung volumes.

1. Bronchodilators

In placebo controlled trials, both short- (albuterol; ipratropium; oxitropium) and long-acting bronchodilators (formoterol; salmeterol; tiotropium) deflate the lung - as measured by an increase in IC or by a corresponding decrease in FRC27-33. These benefits can be observed at rest and/or during exercise. For example, in a recent study, O’Donnell and colleagues34 reported that the combination of fluticasone propionate (250 µg) and salmeterol (50 µg) significantly reduced lung hyperinflation at rest and during constant work exercise after eight weeks of therapy compared with placebo.

Not surprisingly, the benefits of medical volume reduction with pharmacotherapy are greater in those patients with greater degrees of static hyperinflation (i.e., hyperinflation demonstrated while the patient is at rest). For example, Newton et al.31 reported greater changes in IC, RV, and FRC after inhalation of albuterol in patients who had severe hyperinflation (TLC > 133% predicted) compared to those with moderate hyperinflation (115% predicted < TLC < 133% predicted). DiMarco and colleagues35 found that the magnitude of the increase in IC after four different bronchodilators was greater in those patients (n = 12) with resting IC < 80% predicted compared with patients (n = 8) who had IC > 80% predicted. Boni et al.29 found that IC increased significantly only in the 11 patients who had EFL, but not in the nine patients who were non-flow limited.

2. Helium-oxygen mixture

As a low density gas, helium can reduce the resistance drop associated with turbulent air flow. Palange and colleagues36 reported that patients with COPD (n = 12; FEV1 = 38 ± 10% predicted) achieved increases in IC (Δ = 200 ml) at exercise isotime, in peak VE (Δ = 2.8 l/min), and in exercise endurance time (Δ = 4.8 min) when breathing heliox (a mixture of 79% helium and 21% oxygen) compared with room air. Adding to this information, Eves and colleagues37 demonstrated that combining helium and hyperoxia delayed dynamic hyperinflation and improved respiratory mechanics in 10 male patients with COPD (FEV1 = 47 ± 17% predicted).

3. Oxygen

The inhalation of oxygen reduces ventilatory drive (probably via peripheral chemoreceptors), thereby decreases respiratory rate at iso-work levels. This beneficial effect is seen even in COPD patients without significant hypoxemia at rest or during exercise. As stated earlier, higher respiratory rates, such as from exercise, often lead to dynamic hyperinflation in these patients. By promoting a lower respiratory rate, oxygen therapy will allow patients more time to exhale and empty the lungs,
thereby reducing dynamic hyperinflation. Thus, oxygen supplementation indirectly reduces lung volumes in hyperinflated patients with COPD.

4. Rehabilitative exercise training

Porszasz and colleagues\textsuperscript{39} reported that patients with COPD achieved decreases in minute ventilation ($V_E$, $\Delta = 2 \text{l/min}$) and in respiratory frequency ($\Delta = 3 \text{breaths/min}$) at exercise isotime after seven weeks of high intensity exercise training compared to pre-training results. This was accompanied by an increase in IC ($\Delta = 130 \text{ml}$) at isotime levels after training. The latter indicates that exercise training results in less ventilatory demand at identical work levels, and this decreased ventilatory demand allows for a lower respiratory rate and more time for exhalation, thereby reducing lung volumes.

Lung Volume Reduction Surgery (LVRS)

The National Emphysema Treatment Trial (NETT) is the largest investigation of LVRS. NETT compared the effects of lung volume reduction surgery to optimal medical care in 1,218 patients with severe airflow limitation (post-bronchodilator FEV$_1 = 27 \pm 7\%$ predicted) and radiological evidence of moderate-severe emphysema\textsuperscript{40}. Severe hyperinflation was present with TLC of $128 \pm 15\%$ predicted and RV of $222 \pm 49\%$ predicted. Physiologic features including RV did not predict outcomes from surgery.

Although LVRS did not alter overall survival at two years, differential risks and benefits were identified in subgroups of subjects. Logistic regression analyses demonstrated that two features were predictive of survival – distribution of emphysema and exercise capacity. Subjects with upper lobe predominant emphysema and low exercise capacity had better survival after LVRS (risk ratio for death = 0.47; $p = 0.005$), whereas those with non-upper lobe predominant emphysema and high exercise capacity had a higher mortality after LVRS (risk ratio for death = 2.06; $p = 0.02$)\textsuperscript{41}. Longer term follow-up demonstrated an overall survival advantage for all patients who received LVRS compared with medical therapy with a 5 year risk ratio for death of 0.86 ($p = 0.02$)\textsuperscript{41}.

LVRS has also been shown to reduce dynamic hyperinflation during exercise testing\textsuperscript{42} and placement of one-way valves in the airways has been shown to reduce operating lung volumes at rest and dynamic hyperinflation during exercise\textsuperscript{43}.

In summary, measures of hyperinflation, such as the IC/TLC ratio and RV, predict survival in patients with COPD. Overdistension or stretch of the lung can promote inflammation and lung injury based on animal and human studies. At least three treatments: oxygen therapy, lung volume reduction surgery, and the combination of fluticasone/salmeterol, which reduce hyperinflation at rest and/or during exercise have been shown to improve survival in patients with COPD.\textsuperscript{40,44,45} We propose that deflation of the lung may be a mechanism whereby these interventions prolong survival in COPD. Prospective testing will be required to prove this.

Altering the course of COPD with current pharmacotherapies

Bronchodilator therapy

Bronchodilators are the mainstay of current drug therapy for COPD and are recommended by current national and international guidelines as first-line therapy in symptomatic patients and those who demonstrate airflow limitation\textsuperscript{19,46,47}. Three classes of bronchodilators – $\beta_2$-agonists, anticholinergics, and theophylline – are currently available and can be used individually or in combination (Table 2). The use of short-acting bronchodilators is currently advocated for relief of symptoms while that of inhaled long-acting bronchodilators is recommended as treatment of choice for maintenance therapy.

Bronchodilators work through their direct relaxation effect on airway smooth muscle cells, although many have non-bronchodilator activities which may contribute to their beneficial effects in COPD\textsuperscript{48}. The acute response to short-acting bronchodilators, does not predict long-term response to maintenance therapy with long-acting agents; consequently failure to respond to one group of bronchodilators does not necessarily reflect the response to agents of the other groups\textsuperscript{49,50}. The efficacy of bronchodilators has traditionally been assessed by the degree of improvement in FEV$_1$. This, however, is seemingly at odds with the poor correlations recognised between change of FEV$_1$ and changes in dyspnea or exercise performance.

An explanation of how symptoms may be improved with bronchodilators, despite modest changes in FEV$_1$, is suggested by the closer correlation of changes in lung volumes (such inspiratory capacity (IC)) to dyspnea and exercise tolerance\textsuperscript{51}. Therefore, the assessment of bronchodilators using indices of hyperinflation or air trapping may provide a better indicator of efficacy\textsuperscript{52} than FEV$_1$. Although changes in lung volumes are independent of changes in FEV$_1$, several studies have demonstrated that the more sustained airway patency offered by long-acting bronchodilators reduces air trapping\textsuperscript{53,54}.

Currently available long-acting bronchodilators have been shown to have significant effects in the long-term management of COPD. The two currently available LABAs – salmeterol and for-
Table 2  Commonly used pharmacotherapies in COPD

| **β**<sub>2</sub>-agonists | Bitolterol | Clenbuterol | Fenoterol | Isoetharine | Levalbuterol | Metaproterenol | Pirbuterol | Salbutamol (albuterol) | Terbutaline | Bambuterol | Formoterol | Salbutamol (albuterol) SR | Salmeterol | Terbutaline SR |
|----------------------------|------------|-------------|-----------|-------------|-------------|----------------|------------|------------------------|------------|------------|------------|--------------------------|------------|----------------| |
| Short-acting                |            |             |           |             |             |                 |            |                        |            |            |            |                          |            |                |
| Long-acting                |            |             |           |             |             |                 |            |                        |            |            |            |                          |            |                |

**Anticholinergics**

<table>
<thead>
<tr>
<th>Short-acting</th>
<th>Ipratropium bromide</th>
<th>Oxitropium bromide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-acting</td>
<td>Tiotropium</td>
<td></td>
</tr>
</tbody>
</table>

**Combination short-acting β<sub>2</sub>-agonists plus anticholinergic in one inhaler**

<table>
<thead>
<tr>
<th>Fenoterol/Ipratropium</th>
<th>Salbutamol/Ipratropium</th>
</tr>
</thead>
</table>

**Methylxanthines**

<table>
<thead>
<tr>
<th>Aminophylline</th>
<th>Bamiphylline</th>
<th>Dyphylline</th>
<th>Theophylline (SR)</th>
</tr>
</thead>
</table>

**Inhaled glucocorticosteroids**

<table>
<thead>
<tr>
<th>Beclomethasone</th>
<th>Budesonide</th>
<th>Ciclesonide</th>
<th>Flunisolide</th>
<th>Fluticasone</th>
<th>Mometasone</th>
<th>Triamcinolone</th>
</tr>
</thead>
</table>

**Combination long-acting β<sub>2</sub>-agonists plus inhaled glucocorticosteroids in one inhaler**

<table>
<thead>
<tr>
<th>Formoterol/budesonide</th>
<th>Salmeterol/fluticasone</th>
</tr>
</thead>
</table>

— have been shown to significantly improve lung function, health status, and symptom reduction, compared with both placebo<sup>53,55–57</sup> and ipratropium<sup>58,59</sup>. The long-acting muscarinic receptor antagonist tiotropium also shows significant improvements in lung function, dyspnoea, exercise tolerance, and health related quality of life in patients with COPD, relative to placebo<sup>32,60,61</sup> and ipratropium<sup>62</sup>. Two more recent studies, specifically designed to explore the potential differences between tiotropium and salmeterol, seem to indicate a greater efficacy of tiotropium than this LABA<sup>63,64</sup>. The use of LABAs and tiotropium have also been shown to decrease the number of exacerbations and time to first exacerbation of COPD<sup>65</sup>

In addition to their prolonged bronchodilation effect, some bronchodilators have other non-bronchodilator activities that may potentiate their beneficial effects in the treatment of COPD. LABAs exert several effects that may be of clinical relevance<sup>48</sup>. These include inhibition of airway smooth muscle cell proliferation and inflammatory mediator release, as well as non smooth-muscle effects, such as stimulation of mucociliary transport, cytoprotection of the respiratory mucosa, and attenuation of neutrophil recruitment and activation. However, many of these effects have only been described in vitro and in animal studies. Theophylline has also been shown to exert several non-bronchodilator effects which may enhance its effects in COPD<sup>66</sup>. None of the currently available bronchodilators has yet been shown to alter the natural history of COPD over time. However, a large prospective multinational study, the UPLIFT study, is currently underway to investigate the long-term effect of tiotropium on the decline of lung function in patients with COPD<sup>67</sup>. 

**Bronchodilator combination therapy**

For patients whose conditions are not sufficiently controlled with bronchodilator monotherapy, current guidelines recommend combining medications of different classes, in particular an inhaled anticholinergic with a β<sub>2</sub>-agonist, which seems to be a convenient way of delivering treatment and obtaining better results<sup>19,46,47</sup>. Cell signalling through muscarinic M<sub>3</sub> receptors in airway smooth muscle cells is well detailed at a molecular level, and is distinct to those of β<sub>2</sub>-agonists<sup>68,69</sup>. Thus, there is potential for the two drugs to combine additively. Moreover, it has been documented that β<sub>2</sub>-adrenoceptors also mediate inhibition of cholinergic neurotransmission in isolated bovine trachea, through a mechanism involving activation of K<sub>Ca</sub> channels rather than adenylyl cyclase<sup>70</sup>. It is not a surprise, therefore, that large studies have demonstrated that the combination of the short-acting β<sub>2</sub>-agonist salbutamol with the short-acting anticholinergic ipratropium is superior to either single agent alone<sup>71</sup>. More recently, some trials have highlighted that LABAs may represent the most effective option for combination therapy with an anti-muscarinic agent<sup>72</sup>. Considering that formoterol provides a greater degree of early bronchodilation (in the first 2 hours)
than tiotropium and comparable bronchodilation over 12 hours\textsuperscript{73}, the bronchodilator effect of single doses of formoterol 12 µg and tiotropium 18 µg, and formoterol 12 µg + tiotropium 18 µg given together was examined in stable COPD\textsuperscript{74}. Formoterol and tiotropium appeared complementary. In fact tiotropium ensured prolonged bronchodilation and formoterol added fast onset and greater peak effect. Unfortunately, patients only received a single dose of formoterol even though FEV\textsubscript{1} was measured over 24 hours. Combination treatment demonstrated numerical but not statistically significant differences compared with the single treatments and this is likely because the study was underpowered to show a significant difference between treatments. Another study, which investigated the potential additive effect of a second long-acting bronchodilator in patients receiving a first long-acting bronchodilator\textsuperscript{75}, showed that the additive effect does not depend on which type of bronchodilator is administered first.

In a third study, the administration of single doses of 18 µg tiotropium, 50 µg salmeterol, or 18 µg tiotropium + 50 µg salmeterol supported the possibility of combining tiotropium and salmeterol in patients suffering from stable COPD, but excluded the once-daily co-administration of the two drugs\textsuperscript{76}. It was also observed that the onset of action of the two drugs was faster when they were combined considering that both agents have a slow onset of action.

More recently, van Noord et al.\textsuperscript{77} explored the effects elicited by 6 weeks of treatment with tiotropium 18 µg once-daily in the morning, formoterol 12 µg twice a day, and tiotropium 18 µg + formoterol 12 µg once-daily in the morning in patients suffering from moderate-to-severe COPD. Patients receiving combination treatment had a greater improvement in FEV\textsubscript{1} and FVC compared with those receiving the individual agents over 24 h. Significantly better improvements in morning and evening PEF and daytime (but not night-time) rescue salbutamol use were also observed.

A more recently completed clinical trial, which enrolled 847 patients with stable COPD treated for 24 weeks with formoterol 10 µg twice a day, tiotropium 18 µg once-daily, tiotropium plus formoterol or placebo, showed that for selected endpoints (speed of onset of bronchodilation), formoterol plus tiotropium combination therapy was significantly more effective than either monotherapy\textsuperscript{78}. For some variables (notably, FEV\textsubscript{1} 2 hours post-dose, and exacerbations needing additional treatment), combination therapy showed an advantage which was not statistically significant. For many efficacy variables in the study (e.g. bad days’ and ‘exacerbation days’ from diary symptoms, symptom-free days, symptom scores, quality of life [QoL]), the combination and monotherapies were not significantly different.

Furthermore, it has also been documented that for patients suffering a mild-to-moderate acute exacerbation of COPD, combination therapy with formoterol and tiotropium may provide faster and greater peak and overall bronchodilation, with improvement in oxygen saturation\textsuperscript{79}. In this study, both single agents had a shorter duration than expected, perhaps because of increased airways inflammation during an exacerbation – however, the combination improved FEV\textsubscript{1} for 24 h. Further studies are needed to explore the use of these agents in acute exacerbations of COPD.

**LABA + inhaled corticosteroid combination therapy**

The physiologic and clinical benefits of LABAs have been shown to be enhanced when administered in conjunction with inhaled corticosteroids (ICS)\textsuperscript{80}. LABA and ICS combination products have been shown to improve lung function, symptoms, health status and reduce exacerbations in patients with moderate to severe COPD. The recently completed three year TORCH study is the first study to demonstrate a long-term benefit of pharmacotherapy in COPD patients.\textsuperscript{45} The combination of salmeterol/fluticasone propionate had a 17.5% relative risk reduction of mortality compared to placebo (p=0.052). This effect, although of borderline statistical significance, is clinically important and comparable to that of statins in chronic heart disease and smoking cessation in COPD. In addition to a clinically important effect on mortality, the combination of salmeterol/fluticasone propionate significantly decreased exacerbations moderate and severe exacerbations (25% annual reduction of moderate to severe exacerbations, NNT= 4, P<0.001), improved quality of life and function compared to placebo and its components, salmeterol and fluticasone propionate given as monotherapy.

An intriguing short term trial (6-week treatment) has shown that combination therapy with formoterol and tiotropium provides superior bronchodilator effects measured by post-medication FEV\textsubscript{1} than combined treatment with salmeterol and an ICS\textsuperscript{81}. However, another study has documented that the improvement in pulmonary function, expressed as a change in FEV\textsubscript{1}, did not differ between tiotropium and salmeterol/fluticasone propionate, while the simultaneous administration of the two treatments provided superior improvements in trough FEV\textsubscript{1} compared to therapy with the other
two therapeutic regimens given alone. This is an interesting finding, but current data do not allow to establish whether the improvements in lung function demonstrated by combining fluticasone propionate/salmeterol and tiotropium in severe-to-very severe COPD was linked to the effect of the combination of two long-acting bronchodilators or due to a synergistic interaction between the ICS and the long-acting bronchodilators.

Safety of current therapy in COPD

The long-term safety (>3 years) of currently used long-acting bronchodilators needs further studies, however short-term studies (<1 year) have consistently described the safety of these agents when used within their approved dosage. While the safety of long-acting β2-agonists as monotherapy in asthma has recently been questioned, the use of these medications in COPD has generally been described as safe. More recently, data from the recently completed TORCH study, confirms the safety of the chronic use of salmeterol as monotherapy in COPD over three years. Nevertheless, β-agonists should be used with caution in patients with underlying cardiac disorders including ischemic heart disease. Anticholinergic agents should also be used with caution in patients with bladder neck obstruction due to prostatism, and patients with glaucoma. The long-term safety of tiotropium over 4 years is being investigated in the UPLIFT study which is currently underway. A recent meta-analysis, which included randomized controlled trials of at least 3 months duration that evaluated anticholinergic or β2-agonist use compared with placebo or each other in patients with COPD, documented that while inhaled anticholinergics significantly reduced severe exacerbations and respiratory deaths in patients with COPD, β2-agonists were associated with an increased risk for respiratory deaths. However, as highlighted by the authors themselves, this meta-analysis had several limitations, the fact that limits the validity of its results. The long-term safety of inhaled corticosteroids in COPD given over three years was also recently evaluated in the TORCH trial. While the incidence of adverse effects of inhaled corticosteroids on the bone, eye and other systems were not higher than those seen in the placebo treated patients, there was a reported increased incidence of pneumonia. This observation needs to be further evaluated in future studies.

Future directions

Bronchodilators are still central in the symptomatic management of COPD. For this reason, the current opinion is that it will be advantageous to develop inhalers containing combination of several classes of long-acting bronchodilator drugs in an attempt to simplify treatment regimes as much as possible. The investigational therapies for COPD discussed above have shown promising results. It is likely that the development of once-daily dual-action ultra LABA + LAMA combination products may serve as a basis for improved ‘triple therapy’ combinations through co-formulation with novel ICS. In the light of the results of the TORCH study, we believe that a triple once-daily combination of LABA, LAMA and ICS might bring a real advantage over the existing therapies for patients with COPD.

Conflict of interest statement

M Cazzola has received fees for speaking and consulting and/or financial support for attending meetings by Abbott, AZ, Boehringer Ingelheim, Chiesi Farmaceutici, Dey, GSK, Menarini Farmaceutici, Novartis, Nycomed, Pirri, Pfizer and Sanovel.

NA Hanania has received research grant support and is a consultant or speaker for GSK, Boehringer Ingelheim, Sepracor, Dey, Novartis and AZ.

PW Jones has received lecture and consulting fees from GSK, AZ, Bayer, Roche, Spirilation, Almirall and Boehringer.

DA Mahler has received grants from Boehringer-Ingelheim, GSK and Novartis, and has served on advisory boards for AZ, GSK, Novartis, Schlering-Plough and Sepracor.

B Make has participated in medical advisory boards for GSK, Boehringer-Ingelheim, Pfizer, Forrest and Schering Plough; received honoraria for lectures from GSK, Boehringer-Ingelheim, and Pfizer.; participated in multi-center studies funded by GSK, Boehringer-Ingelheim, Pfizer, and Schering Plough; and served as a consultant for Chiesi.

J Ohar has served as a speaker for Pfizer and involved with Pfizer 2008 Advisory Board Medical & Academic Partnership Grants

S Rennard has received laboratory and industry grants from Almirall, Altana, Astellas, Centocor, GSK, Nabi, Novartis and Pfizer. He has served on consultancy and advisory boards for Adams, Almirall, Altana, AZ, Bend, Biolipox, Centocor, Critical Therapeutics, Dey, GSK, ICOS, Johnson & Johnson, Novartis, Ono Pharma, Pareagenix, Pfizer, Roche, Sankyo, Sanofi, Schering-Plough and Talecris. He has also so served as a speaker for AZ, Boehringer Ingelheim, GSK, Otsuka and Pfizer.
References


61. Brichetto L, Song P, Crimi E, Reher K, Brusasco V.
Modulation of cholinergic responsiveness through the \( \beta \)-adrenoceptor signal transmission pathway in bovine trachealis. *J Appl Physiol* 2003;95:735–41

71. COMBIVENT Inhalation Aerosol Study Group. In chronic obstructive pulmonary disease, a combination of ipratropium and albuterol is more effective than either agent alone. An 85-day multicenter trial. *Chest* 1994;105:1411–9


78. Vogelmeier CF, Harari SA, Fonay K, Beier J, Overend T, Till D, Stenglein S, Oldani V. Formoterol and tiotropium both improve lung function in stable COPD patients, with some additional benefit when given together [abstract]. *Eur Respir J* 2006;28 Suppl 50:429s


