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REVIEW

COPD: what is the unmet need?

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Chronic obstructive pulmonary disease (COPD) is now recognized as a major source of ill health around the world with an important impact on both developed and developing economies. The emphasis in research has shifted from a purely physiological focus that mainly considered how airway smooth muscle tone can be modulated to improve lung emptying. Although long-acting inhaled β-agonist and antimuscarinic antagonists have improved clinical management for many symptomatic patents, there is increasing attention being paid to the inflammatory component of COPD in the airways and lung parenchyma and to its close association with other diseases, which cannot simply be attributed to their having a common risk factor such as tobacco smoking. This clinical review is intended to identify not only those areas where pharmacological treatment has been successful or has offered particular insights into COPD but also to consider where existing treatment is falling short and new opportunities exist to conduct original investigations. A picture of considerable complexity emerges with a range of clinical patterns leading to several common end points such as exacerbations, exercise impairment and mortality. Defining subsets of patients responsive to more specific interventions is the major challenge for the next decade in this field.
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Abbreviations: COPD, chronic obstructive pulmonary disease; TORCH, Towards a Revolution in COPD Health

Introduction

There is general agreement that the prevalence of chronic obstructive pulmonary disease (COPD), the term now used to encompass both chronic bronchitis and emphysema associated with chronic poorly reversible airflow obstruction (Rabe *et al.*, 2007), is increasing across both the developed and the developing world (Chapman *et al.*, 2006; Buist *et al.*, 2007). This is both surprising and disappointing as it is over 50 years since the pioneering observations of Doll and Hill (Doll *et al.*, 1994) that related not only deaths from lung cancer and heart disease to tobacco smoking but also identified that what was then called chronic obstructive bronchitis was also more likely to lead to the deaths of doctors who smoked than those who did not. The continuing problem of COPD reflects not only our failure to effectively learn the lessons of the past, particularly in terms of primary prevention, but also the beneficial effects of persuading many people in Western countries to stop smoking. This has been an important contributory factor to the decline in deaths due to ischaemic heart disease. In smokers who quit, there is a progressive reduction in the risk of having a new myocardial infarction as the years following smoking cessation increase. By contrast in COPD patients, particularly those who stop smoking when they have developed symptoms, the structural damage that leads to airflow obstruction persists. There is growing evidence that the inflammation associated with COPD is present in ex-smokers (Hogg *et al.*, 2004; Gamble *et al.*, 2007) and it should be no surprise that the rate of decline of lung function remains abnormal, even in patients who quit some time earlier. As our population ages so the cohort of people who were ex-smokers or those relatively insensitive to its other deleterious effects increases and many of these patients develop COPD. They present a major burden on our health-care system and are likely to do so for several decades to come. Understanding their clinical need and considering what we can do to modify both their disease and its impact are now a major focus of attention in health systems across the world.

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What are the needs?

From a clinical perspective, there are now data about the main concerns of COPD patients (Rennard *et al.*, 2002; Haughney *et al.*, 2005). Population studies have shown among those hospitalized with COPD, 50% are re-admitted on a future occasion and ~13% of a population of COPD

patients with a range of disease severity will be hospitalized in a 3-year period (Soler-Cataluna *et al*., 2005; Calverley *et al*., 2007). In total, 60% of all COPD patients will report some limitations in their daily activity, with 45% being unable to work and 75% complaining of difficulty climbing stairs (Rennard *et al*., 2002). Patients who have COPD have globally impaired quality of life and specifically, their health status with respect to their lung symptoms is worse than that of healthy subjects (Seemungal *et al*., 1998; Spencer *et al*., 2001). Exacerbations are particularly concerning and there are structured data now showing that during an exacerbation, patients feel that they may die, feel as though they are suffocating and become depressed after the event and at the prospect of further events occurring. Understandably, these seriously affect their family and personal relationships (Kessler *et al*., 2006).

On the basis of these data and others, the major unmet clinical needs are summarized in Table 1 from both the patients' and the clinicians' perspectives. Two of these areas are particularly worth noting. Patients understandably want better control of the symptoms that impact on their life, especially breathlessness and also chronic coughs, sputum production and general fatigue. With our existing treatment, it is clear that this goal can be accomplished by combining different types of therapy, for example, drug treatment with physical therapy such as pulmonary rehabilitation (Rabe *et al*., 2007). However, this does pose particular problems for people who wish to develop new pharmacological therapies. The current regulatory models based on placebo-controlled comparisons become especially difficult when there is no agreed metric for the end point, for example, symptoms or the occurrence of an exacerbation and when the adjunctive therapy can vary in its quality, for example, the frequency and character of pulmonary rehabilitation Cazzola *et al*., 2008). To deal with this difficulty, most clinical trials have had to increase their sample size to look for a signal. Moreover, this has made it harder to gain a true idea of the magnitude of the effect of an individual therapy when compared with its effect as part of a mixed treatment regimen.

A further and now very current issue is the extent to which COPD predicts or indeed promotes the development of other diseases, some of which can produce symptoms that worsen or mimic those of COPD. There is good evidence that ischaemic heart disease, osteoporosis and lung cancer all occur more frequently in COPD patients than in other people with a similar risk profile without evidence of COPD. Peripheral muscle weakness and loss of muscle mass are frequent and prognostically important findings in COPD, although this may reflect loss of function due to immobility rather than specific myopathic processes. Patients are less directly aware of these problems but this is going to be an important area in patient management in the coming decades.

Table 1 Unmet needs in COPD

Unmet needs of the COPD patient
- More effective diagnosis and primary prevention
- Better symptom control
- Fewer exacerbations
- Slowing of disease progression
- Better life expectancy
- Less systemic disease secondary to COPD and fewer co-morbidities

Unmet needs of the medical community
- Optimizing disease prevention
- Improving symptom control
- Preventing exacerbations and decreasing their clinical impact
- Preventing disease progression
- Reducing disease-related mortality
- Identifying systemic effects and co-morbidities

Abbreviation: COPD, chronic obstructive pulmonary disease.

Disease prevention

Primary prevention of COPD has quite correctly focused on tobacco control and real progress has been made in Europe and North America. Tobacco use still shows a strong social gradient between the most and least affluent members of society and there are real concerns about the increase in smoking among younger women and the difficulties that they have in quitting. Nonetheless, the main burden of tobacco use is now in the rapidly developing economies of China, India and Southeast Asia where state sponsorship of tobacco companies remains at odds with the desire to improve national health. The Global initiative in chronic Obstructive Lung Disease (GOLD) definition of COPD emphasizes the importance of persisting airflow obstruction associated with inflammation and occurring as a consequence of inhaled noxious substances (Rabe *et al*., 2007). Although tobacco is the commonest of these, there is now clear evidence from South America (Perez-Padilla *et al*., 1996) and especially from southern China (Yin *et al*., 2007) that exposures to biomass fuels predominantly wood smoke in poorly ventilated environments can produce significant degrees of airflow obstruction.

Secondary prevention remains an important focus. Brief advice is a cost-effective way of encouraging smoking cessation but the quit rate after any given contact is relatively low (Srivastava *et al*., 2006). COPD patients who smoke appear to be relatively resistant to other treatments, possibly reflecting the fact that the most susceptible will have quit already before they enter a study. Nonetheless, treatment with bupropion does increase the quit rate of smoking in COPD patients (Tashkin *et al*., 2001). The acceptability of this drug has been undermined by public concerns about cardiac risk but a new and more effective option is now becoming available in the form of varenicline. There are good data in healthy smokers to show that this agent is superior both to standard advice and to bupropion (Gonzales *et al*., 2006). Data extending its use to COPD are awaited with interest. Other forms of secondary prevention, particularly when biomass fuel exposure is involved, are also effective. Simply fitting better ventilation can have an impact on the number of people who have COPD as has been shown in one study in China (Chapman *et al*., 2005) and the long-term investments of this kind are likely to be highly cost-effective, and other studies that extend these approaches are urgently needed.

Symptom control

Clinical practice for many years has relied on the use of short-acting bronchodilator drugs such as salbutamol and ipratropium to reduce self-reported breathlessness in COPD. There are abundant empirical data that exercise performance and breathlessness at the end of exercise can be increased with these therapies (O'Donnell, 2006). By contrast, there is remarkably little information about cough and sputum production, mainly due to a lack of adequate validated questionnaires that capture this information. For many clinicians, the use of a bronchodilator drug in COPD seemed to be contradictory as the immediate improvement in forced expiratory volume in 1 s (FEV_1) and objective measure of its efficacy bear little, if any, relationship to the patient's self-reported symptoms. The reasons for this have now been established and it is clear that the main effect of bronchodilator drugs is to produce small but important improvement in lung emptying and as a result, decrease the operating lung volumes of the COPD patient. A reduction in inspiratory capacity, which measures the end expiratory lung volume, of around 200–250 ml is quite common after bronchodilator drug use (Newton *et al.*, 2002). This translates into a 20–25% improvement in exercise performance in those whose lung function is below 50% of predicted. As there is a reduction in dynamic hyperinflation as a consequence of the improvement in resting lung volumes, the degree of breathlessness experience for any given intensity of exercise is less (O'Donnell *et al.*, 2004a, b).

However, some patients do not benefit from bronchodilator treatment and it is common practice to change them from one class of drug to another to see if they fare better. The reasons for this are now becoming clearer as a careful analysis of the breathing pattern during exercise after salbutamol have shown (Aliverti *et al.*, 2005). In this study, the patients who improved their exercise performance on the cycle ergometer were those in whom chest wall volume fell after bronchodilator use but then increased during exercise. By contrast, those patients who tried to decrease lung volume further when they exercised after bronchodilator use had a worse exercise performance. Thus, it may take patients some time to adapt appropriately to the physiological changes that bronchodilator drugs can produce. Other data looking at the effect of anticholinergic drugs on exercise performance have shown that the ability to increase exercise tolerance, at least in the laboratory setting, depends on which symptom is limiting exercise in the first place. In some patients, objectively demonstrated skeletal muscle fatigue in the legs limits exercise and unsurprisingly, bronchodilator drugs do not improve this (Pepin *et al.*, 2005).

Not all treatments are based on bronchodilatation. Exercise performance can be improved by breathing supplementary oxygen that reduces respiratory drive and probably decreases metabolic carbon dioxide production (O'Donnell *et al.*, 2001). Altering the density of the gas the patient breathes by substituting helium for nitrogen has a similar effect and the combination of the two enhances exercise performance (Laude *et al.*, 2006), probably by reducing the work of breathing (Peters *et al.*, 2006). Unfortunately, this approach is limited both by the expense of helium mixtures and the difficulty in obtaining a tight-fitting mask that can deliver this without dilution with room air. Nonetheless, there may be circumstances, particularly in acute care, where such an approach may be valuable.

Ultimately, the combination of different treatments such as bronchodilators and oxygen do seem to be at least additive (Cukier *et al.*, 2006; Peters *et al.*, 2006) and this is the basis of the multimodality approach to treating COPD. However, there are some reasons to be cautious. Most evaluations of treatment are conducted in the hospital laboratory and just because the patient can walk farther does not mean that they will do so. Recent data from our laboratory suggest that improvements in exercise performance during pulmonary rehabilitation are not necessarily reflected by how much exercise the individual takes at home (Walker *et al.*, 2008).

Pulmonary rehabilitation produces large improvements in patient well-being in those who complete the treatment but this tends to decline over time (Ries *et al.*, 2003). Future studies will need to determine how this relates to daily activity at home and whether it can be improved by other interventions. At present, dietary supplements have been shown to improve respiratory muscle strength in patients who are not too wasted (Steiner *et al.*, 2003), whereas creatine has been adopted from athletic practice to show some small but potentially interesting improvements in muscle function (Fuld *et al.*, 2005). Whether this use of nutriceuticals can be adapted further to reduce the symptoms of COPD patients is a continuing challenge.

Exacerbations of COPD

COPD exacerbations are important predictors of patient well-being (Spencer *et al.*, 2004) and of the likelihood of patients dying (Soler-Cataluna *et al.*, 2005). They range from unreported increases in patients' symptoms (Seemungal *et al.*, 2000) through to periods requiring ventilatory support, which may be non-invasive or involving intubation. In general, the severity of the patient's underlying lung disease determines the clinical picture rather than differences in the factors that precipitate exacerbations. The treatment of acute episodes has changed little over the last two decades with the exception of the introduction of non-invasive ventilation, which has had important beneficial effects for those with respiratory failure (Lightowler *et al.*, 2003).

Prevention of these episodes has focused on reducing the chances of acquiring viral or viral infections such as influenza (Nichol *et al.*, 1999) or pneumococcal pneumonia, which does appear to be effective in patients with more severe symptomatic COPD (Alfageme *et al.*, 2006). Medication originally intended for symptom reduction such as bronchodilator drugs, both β-agonists and anticholinergic, reduce the number of reported COPD exacerbation (Scott *et al.*, 2006), whereas there is a large body of data suggesting that the same is true for inhaled corticosteroids (Calverley *et al.*, 2007). Finding an appropriate way to quantify the magnitude of these effects has proven particularly taxing, as the events themselves are infrequent and each individual has

their own *a priori* risk of developing an exacerbation (Suissa, 2006). Appropriate statistical models have been developed and when applied to large data sets, such as the recently reported Towards a Revolution in COPD Health (TORCH) trial (Calverley *et al*., 2007), it is clear that both long-acting bronchodilators and inhaled steroids have a beneficial effect, which is rather greater when the two are combined in the same inhaler. A direct comparison of long-acting anticholinergic and combinations of this kind has now been reported (Wedzicha *et al*., 2008). The overall exacerbation rates in this study were similar, although more patients randomized to receive the tiotropium withdrew during the study than those on the combination treatment. Further data in more severe patients have been reported from Canada (Aaron *et al*., 2007). Here, all patients received tiotropium but the best health status and lowest hospitalization rates occurred in those who received tiotropium, salmeterol and the inhaled steroid. Other, better powered studies will be needed to determine whether this is reflected in self-reporting exacerbation frequency.

Important as the study of exacerbations are, it would move forward greatly if new therapeutic approaches were developed to address it. The extent to which these can be added together is not yet clear. Antioxidant drugs reduce exacerbations in patients not receiving inhaled steroids (Decramer *et al*., 2005). However, the exacerbations that corticosteroids prevent seem to be those associated with oral corticosteroid treatment rather than those which are treated with antibiotics. The role of prophylactic antibiotics in COPD is now being revisited and is likely to be important.

Disease progression

Although smoking cessation reduces the subsequent decline in lung function of COPD patients, treatment with the short-acting bronchodilator drug ipratropium did not, at least over the 5 years of the original Lung Health Study (Anthonisen *et al*., 1994). There are pathological data that show that as lung function worsens, so do the degree of thickening and fibrosis of the small airways (Hogg, 2004). The relationship of lung function deterioration to the severity of emphysema defined by computed tomography is less clear even in α-1-antitrypsin deficiency (Dirksen *et al*., 1999). As the intensity of inflammation per unit volume of tissue rises with worsening GOLD stage, it is not unreasonable to believe that anti-inflammatory treatment might modify disease progression (Hogg *et al*., 2004), and in the late 1990s a series of studies that were large for the time were reported that looked at the effects of different inhaled corticosteroids and the rate of decline of lung function in COPD. They encompassed a range of disease severity from very mild disease (Vestbo *et al*., 1999) through to quite severe disease under hospital review (Burge *et al*., 2000). None of these studies showed a significant difference in lung function decline over the 3 years that they were conducted, although in all cases treatment was associated with a somewhat slower rate of decline than being randomized to placebo. Two conflicting meta-analyses and a pooled data analysis have since been reported (Alsaeedi *et al*., 2002; Sutherland *et al*., 2003; Soriano *et al*., 2007).

More recently, data from the TORCH study have been reported that suggests treatment with bronchodilator corticosteroid or the combination has a beneficial effect on the rate of decline of lung function compared with patients receiving placebo (Celli *et al*., 2007). The TORCH data set is substantially larger than any of the other studies and deals with patients with worse lung function than those reported earlier. The forthcoming Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) trial comparing tiotropium with placebo has as its primary outcome the rate of decline of lung function. If the TORCH data are correct, then one would anticipate that a long-acting bronchodilator alone will also have a beneficial effect on this index of disease progression. However, it is clear that to identify such an effect requires very large numbers of patients studied for relatively long periods. There is an urgent need for more manageable surrogate markers that could identify candidate treatments that might have this beneficial effect (Cazzola *et al*., 2008).

Mortality

The ability of drugs to reduce patients' symptoms and improve their health status makes it reasonable to ask whether the duration of their lives as well as its quality can be improved. Historically, relatively few interventions in COPD have been studied in this way. The long-term follow-up of the original Lung Health Study cohort comparing people randomized to an intensive smoking cessation programme or usual advice showed that patients in the smoking cessation programme had a lower long-term mortality (Anthonisen *et al*., 2005), which is to be expected as more of these were successful quitters. Correcting chronic hypoxaemia with domiciliary oxygen treatment had a dramatic and significant effect in reducing mortality in patients with very severe disease (Anonymous, 1980, 1981). However, these patients are relatively infrequent in routine practice as are those with severe emphysema affecting the upper lobes of their lungs who prove unresponsive to pulmonary rehabilitation. This subset of patients appears to have a mortality benefit when randomized to lung volume reduction treatment (Fishman *et al*., 2003), but the cost-effectiveness of this approach has been disputed (Ramsey *et al*., 2003).

Several studies have used databases to relate therapy with drugs designed to diminish symptoms and exacerbation to the patient's risk of dying. This has proved a highly controversial field with small differences in methodology producing potential spurious results (Suissa, 2004). The most rigorously performed of these studies has suggested that there would be a benefit from using a combination of an inhaled corticosteroid and a long-acting β-agonist compared with either the components or placebo (Soriano *et al*., 2002) and this was the hypothesis for what was prospectively tested as the main outcome in the TORCH study.

The results of the primary outcome of this trial are now well known (Calverley *et al*., 2007). After adjustment for the

interim safety analyses, the significance level between the salmeterol–fluticasone combination and placebo approached significance ($P=0.052$). The interpretation of such a marginal *P*-value has proven controversial and is discussed at length in the paper. Nonetheless, taken with the results of the other measures that are known to track mortality, it seems likely that a real effect of treatment on mortality exists. Improvements were seen in both cardiovascular and pulmonary mortality but there was no beneficial effect of treatment in patients receiving inhaled corticosteroid, which was unexpected given the database results and should lead us to be cautious when interpreting similar data in other contexts. Again, the message is that when a large number of variables impact on a patient population, very large numbers of patients have to be followed for a long period and the expense of conducting such study becomes prohibitive (Calverley and Rennard, 2007). The mortality data in the UPLIFT study will be especially important as this is likely to be the only very large COPD trial reporting for several years.

Systemic effects and co-morbidity

The recognition that COPD is associated with increased cardiovascular mortality and morbidity, which cannot be explained simply by smoking has grown from epidemiological studies (Sin *et al*., 2006) and also from more direct observations about abnormalities in the pulse wave velocity of COPD patients (Sabit *et al*., 2007). Arterial stiffness tracks other markers of systemic disease, such as reduced bone mineral density, a common problem in COPD (Sin *et al*., 2003; Bolton *et al*., 2004). COPD is associated with an increased risk of developing lung cancer (Turner *et al*., 2007) and this has been proposed as a potential screening strategy to identify patients at high risk of this disease. Several complications associated with COPD can be anticipated from its known biological effects. In patients with advanced disease, a low arterial oxygen tension will promote the development of pulmonary hypertension and secondary polycythaemia. Inactivity is associated with muscle wasting, although there is a continuing debate as to whether there is a specific COPD myopathy (Debigare *et al*., 2003). At present the balance of evidence is against this. Nonetheless, nutritional depletion is an important diagnostic feature and muscle weakness is an independent marker of COPD mortality (Swallow *et al*., 2007).

Categorizing patients in a way that takes account of these co-morbidities and so addresses the needs of medication in the real COPD population is going to be important in future studies. Clearly, there are hazards for investigators who wish to understand the interaction of new treatment and co-morbidity. However, there is a strong feeling in the medical community that guidance which is derived from clinical trials should be based on treatment in the kinds of patient groups they see in practice rather than those most suitable for regulatory studies. On the positive side, treatments with multiple effects, for instance statin therapy, may prove beneficial for COPD patients above and beyond their anticipated cardiovascular benefits (Mancini *et al*., 2006). At present, the evidence for such an effect is largely epidemiological with the reasonably reproducible observation that patients receiving statins were less likely to die or be hospitalized with COPD than other COPD patients not treated in this way. The pleiotropic anti-inflammatory properties of statins make this an attractive hypothesis but as yet there are no clinical trial data that directly tests the hypothesis that these agents have a beneficial effect. Studies looking at this issue are being planned.

The unmet need of the scientific community

The diagnosis of COPD identifies a fairly consistent group of patients characterized by airflow obstruction and progressive symptoms. This reflects the impact of pathological damage within the lungs, which varies from individual to individual. There is a continuing search for distinctive phenotypes of COPD patients who will prove responsive to one treatment rather than another. Considerable effort has gone into excluding any patient who might show an overlap with asthma whether defined by clinical, physiological or inflammatory criteria. This may be unhelpful in the long run as many such overlap patients are likely to exist in normal clinical practice and our phenotypes for asthma are less robust than is sometimes imagined. The search for discrete COPD-associated phenotypes remains a reasonable goal but analysis at the level of physiology, function and symptoms does not seem to relate well to more basic processes identified from airway biopsies or from tissues or cells exposed to tobacco smoke or some surrogate injury. Similarly, the development of predictive bio-markers has become something of a 'holy grail' in COPD research and there have been no shortage of candidates. However, in no case has a reliable, reproducible and predictive blood or sputum marker been developed, although efforts continue to achieve this. This issue has been comprehensively reviewed recently as part of an American Thoracic Society/European Respiratory Society (ATS/ERS) taskforce report on clinical outcome markers in COPD (Cazzola *et al*., 2008). Our failure to develop an appropriate animal model of COPD or to distinguish between a pathological process that produces long-term disease progression and the more immediate problems leading to symptomatic patients provides a continuing dilemma for COPD researchers. We are rapidly approaching the limit of what can be achieved by the modulation of airway smooth muscle tone and hence lung emptying, or by decreasing inflammation with existing anti-inflammatory drugs. Long-acting β-agonists appear to be the best drugs and when combined with inhaled corticosteroids can change airway cellularity (Barnes *et al*., 2006). However, the mechanisms operative in real patients are likely to be much more complex than those that can be simplified and analysed by our existing pharmacological probes. New approaches to the relative lack of efficacy of corticosteroids are being developed (Ito *et al*., 2005) and these may lead to better drugs. However, a re-appraisal of the mechanisms that lead to COPD and the clinical stages at which they can be modified is long overdue.

With better intermediate markers of disease activity and a clear understanding of the way in which symptoms relate to

structural change, we would be in a strong position to modify the natural history of COPD and reduce its clinical impact. Although this is a difficult task it should not be beyond us and the continuing burden of COPD across the world will provide the stimulus that should make us address it.

References

Aaron SD, Vandemheen KL, Fergusson D, Maltais F, Bourbeau J, Goldstein R *et al.* (2007). Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med* **146**: 545–555.

Alfageme I, Vazquez R, Reyes N, Munoz J, Fernandez A, Hernandez M *et al.* (2006). Clinical efficacy of anti-pneumococcal vaccination in patients with COPD. *Thorax* **61**: 189–195.

Aliverti A, Rodger K, Dellaca RL, Stevenson N, Lo MA, Pedotti A *et al.* (2005). Effect of salbutamol on lung function and chest wall volumes at rest and during exercise in COPD. *Thorax* **60**: 916–924.

Alsaeedi A, Sin DD, McAlister FA (2002). The effects of inhaled corticosteroids in chronic obstructive pulmonary disease: a systematic review of randomized placebo-controlled trials. *Am J Med* **113**: 59–65.

Anonymous (1980). Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Nocturnal Oxygen Therapy Trial Group. *Ann Intern Med* **93**: 391–398.

Anonymous (1981). Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party. *Lancet* **1**: 681–686.

Anthonisen NR, Connett JE, Kiley JP, Altose MD, Bailey WC, Buist AS *et al.* (1994). Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1. The Lung Health Study [see comments]. *JAMA* **272**: 1497–1505.

Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE (2005). The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. *Ann Intern Med* **142**: 233–239.

Barnes NC, Qiu YS, Pavord ID, Parker D, Davis PA, Zhu J *et al.* (2006). Antiinflammatory effects of salmeterol/fluticasone propionate in chronic obstructive lung disease. *Am J Respir Crit Care Med* **173**: 736–743.

Bolton CE, Ionescu AA, Shiels KM, Pettit RJ, Edwards PH, Stone MD *et al.* (2004). Associated loss of fat-free mass and bone mineral density in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* **170**: 1286–1293.

Buist AS, McBurnie MA, Vollmer WM, Gillespie S, Burney P, Mannino DM *et al.* (2007). International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. *Lancet* **370**: 741–750.

Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK (2000). Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. *BMJ* **320**: 1297–1303.

Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW *et al.* (2007). Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* **356**: 775–789.

Calverley PM, Rennard SI (2007). What have we learned from large drug treatment trials in COPD? *Lancet* **370**: 774–785.

Cazzola M, MacNee W, Martinez FJ, Rabe KF, Franciosi LG, Barnes PJ *et al.* (2008). Outcomes for COPD pharmacological trials: from lung function to biomarkers. *Eur Respir J* **31**: 416–469.

Celli B, Ferguson GT, Anderson JA, Jenkins CR, Jones PW, Vestbo J *et al.* (2007). Salmeterol/fluticasone propionate (SFC) improves lung function and reduces rate of decline over three years in the TORCH survival study. *Proc Am Thorac Soc* **4**: A763 (ref type: Abstract).

Chapman KR, Mannino DM, Soriano JB, Vermeire PA, Buist AS, Thun MJ *et al.* (2006). Epidemiology and costs of chronic obstructive pulmonary disease. *Eur Respir J* **27**: 188–207.

Chapman RS, He X, Blair AE, Lan Q (2005). Improvement in household stoves and risk of chronic obstructive pulmonary disease in Xuanwei, China: retrospective cohort study. *BMJ* **331**: 1050.

Cukier A, Ferreira CA, Stelmach R, Ribeiro M, Cortopassi F, Calverley PM (2006). The effect of bronchodilators and oxygen alone and in combination on self-paced exercise performance in stable COPD. *Respir Med* **101**: 746–753.

Debigare R, Marquis K, Cote CH, Tremblay RR, Michaud A, LeBlanc P *et al.* (2003). Catabolic/anabolic balance and muscle wasting in patients with COPD. *Chest* **124**: 83–89.

Decramer M, Rutten-van Molken M, Dekhuijzen PN, Troosters T, van Herwaarden C, Pellegrino R *et al.* (2005). Effects of *N*-acetylcysteine on outcomes in chronic obstructive pulmonary disease (Bronchitis Randomized on NAC Cost–Utility Study, BRONCUS): a randomised placebo-controlled trial. *Lancet* **365**: 1552–1560.

Dirksen A, Dijkman JH, Madsen F, Stoel B, Hutchison DC, Ulrik CS *et al.* (1999). A randomized clinical trial of alpha(1)-antitrypsin augmentation therapy. *Am J Respir Crit Care Med* **160**: 1468–1472.

Doll R, Peto R, Wheatley K, Gray R, Sutherland I (1994). Mortality in relation to smoking: 40 years' observations on male British doctors. *Br Med J* **309**: 901–911.

Fishman A, Martinez F, Naunheim K, Piantadosi S, Wise R, Ries A *et al.* (2003). A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. *N Engl J Med* **348**: 2059–2073.

Fuld JP, Kilduff LP, Neder JA, Pitsiladis Y, Lean ME, Ward SA *et al.* (2005). Creatine supplementation during pulmonary rehabilitation in chronic obstructive pulmonary disease. *Thorax* **60**: 531–537.

Gamble E, Grootendorst DC, Hattotuwa K, O'Shaughnessy T, Ram FS, Qiu Y *et al.* (2007). Airway mucosal inflammation in COPD is similar in smokers and ex-smokers: a pooled analysis. *Eur Respir J* **30**: 467–471.

Gonzales D, Rennard SI, Nides M, Oncken C, Azoulay S, Billing CB *et al.* (2006). Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. *JAMA* **296**: 47–55.

Haughney J, Partridge MR, Vogelmeier C, Larsson T, Kessler R, Stahl E *et al.* (2005). Exacerbations of COPD: quantifying the patient's perspective using discrete choice modelling. *Eur Respir J* **26**: 623–629.

Hogg JC (2004). Pathophysiology of airflow limitation in chronic obstructive pulmonary disease. *Lancet* **364**: 709–721.

Hogg JC, Chu F, Utokaparch S, Woods R, Elliott WM, Buzatu L *et al.* (2004). The nature of small-airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med* **350**: 2645–2653.

Ito K, Ito M, Elliott WM, Cosio B, Caramori G, Kon OM *et al.* (2005). Decreased histone deacetylase activity in chronic obstructive pulmonary disease. *N Engl J Med* **352**: 1967–1976.

Kessler R, Stahl E, Vogelmeier C, Haughney J, Trudeau E, Lofdahl CG *et al.* (2006). Patient understanding, detection, and experience of COPD exacerbations: an observational, interview-based study. *Chest* **130**: 133–142.

Laude EA, Duffy NC, Baveystock C, Dougill B, Campbell MJ, Lawson R *et al.* (2006). The effect of helium and oxygen on exercise performance in COPD: a randomised crossover trial. *Am J Respir Crit Care Med* **173**: 865–870.

Lightowler JV, Wedzicha JA, Elliott MW, Ram FS (2003). Non-invasive positive pressure ventilation to treat respiratory failure resulting from exacerbations of chronic obstructive pulmonary disease: Cochrane systematic review and meta-analysis. *BMJ* **326**: 185.

Mancini GB, Etminan M, Zhang B, Levesque LE, FitzGerald JM, Brophy JM (2006). Reduction of morbidity and mortality by statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers in patients with chronic obstructive pulmonary disease. *J Am Coll Cardiol* **47**: 2554–2560.

Newton MF, O'Donnell DE, Forkert L (2002). Response of lung volumes to inhaled salbutamol in a large population of patients with severe hyperinflation. *Chest* **121**: 1042–1050.

Nichol KL, Baken L, Nelson A (1999). Relation between influenza vaccination and outpatient visits, hospitalization, and mortality in elderly persons with chronic lung disease. *Ann Intern Med* **130**: 397–403.

O'Donnell DE (2006). Hyperinflation, dyspnea, and exercise intolerance in chronic obstructive pulmonary disease. *Proc Am Thorac Soc* **3**: 180–184.

O'Donnell DE, D'Arsigny C, Webb KA (2001). Effects of hyperoxia on ventilatory limitation during exercise in advanced chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* **163**: 892–898.

O'Donnell DE, Fluge T, Gerken F, Hamilton A, Webb K, Aguilaniu B *et al.* (2004a). Effects of tiotropium on lung hyperinflation, dyspnoea and exercise tolerance in COPD. *Eur Respir J* **23**: 832–840.

O'Donnell DE, Voduc N, Fitzpatrick M, Webb KA (2004b). Effect of salmeterol on the ventilatory response to exercise in chronic obstructive pulmonary disease. *Eur Respir J* **24**: 86–94.

Pepin V, Saey D, Whittom F, LeBlanc P, Maltais F (2005). Walking versus cycling: sensitivity to bronchodilation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* **172**: 1517–1522.

Perez-Padilla R, Regalado J, Vedal S, Pare P, Chapela R, Sansores R *et al.* (1996). Exposure to biomass smoke and chronic airway disease in Mexican women. A case–control study. *Am J Respir Crit Care Med* **154**: 701–706.

Peters MM, Webb KA, O'Donnell DE (2006). Combined physiological effects of bronchodilators and hyperoxia on exertional dyspnoea in normoxic COPD. *Thorax* **61**: 559–567.

Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P *et al.* (2007). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* **176**: 532–555.

Ramsey SD, Berry K, Etzioni R, Kaplan RM, Sullivan SD, Wood DE (2003). Cost effectiveness of lung-volume-reduction surgery for patients with severe emphysema. *N Engl J Med* **348**: 2092–2102.

Rennard S, Decramer M, Calverley PM, Pride NB, Soriano JB, Vermeire PA *et al.* (2002). Impact of COPD in North America and Europe in 2000: subjects' perspective of confronting COPD International Survey. *Eur Respir J* **20**: 799–805.

Ries AL, Kaplan RM, Myers R, Prewitt LM (2003). Maintenance after pulmonary rehabilitation in chronic lung disease: a randomized trial. *Am J Respir Crit Care Med* **167**: 880–888.

Sabit R, Bolton CE, Edwards PH, Pettit RJ, Evans WD, McEniery CM *et al.* (2007). Arterial stiffness and osteoporosis in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* **175**: 1259–1265.

Scott S, Walker P, Calverley PM (2006). COPD exacerbations. 4: Prevention. *Thorax* **61**: 440–447.

Seemungal TA, Donaldson GC, Bhowmik A, Jeffries DJ, Wedzicha JA (2000). Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* **161**: 1608–1613.

Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA (1998). Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* **157**: 1418–1422.

Sin DD, Anthonisen NR, Soriano JB, Agusti AG (2006). Mortality in COPD: role of comorbidities. *Eur Respir J* **28**: 1245–1257.

Sin DD, Man JP, Man SF (2003). The risk of osteoporosis in Caucasian men and women with obstructive airways disease. *Am J Med* **114**: 10–14.

Soler-Cataluna JJ, Martinez-Garcia MA, Roman SP, Salcedo E, Navarro M, Ochando R (2005). Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. *Thorax* **60**: 925–931.

Soriano JB, Sin DD, Zhang X, Camp PG, Anderson JA, Anthonisen NR *et al.* (2007). A pooled analysis of FEV1 decline in COPD patients randomized to inhaled corticosteroids or placebo. *Chest* **131**: 682–689.

Soriano JB, Vestbo J, Pride NB, Kiri V, Maden C, Maier WC (2002). Survival in COPD patients after regular use of fluticasone propionate and salmeterol in general practice. *Eur Respir J* **20**: 819–825.

Spencer S, Calverley PM, Burge PS, Jones PW (2004). Impact of preventing exacerbations on deterioration of health status in COPD. *Eur Respir J* **23**: 698–702.

Spencer S, Calverley PMA, Burge PS, Jones PW (2001). Health status deterioration in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* **163**: 122–128.

Srivastava P, Currie GP, Britton J (2006). Smoking cessation. *BMJ* **332**: 1324–1326.

Steiner MC, Barton RL, Singh SJ, Morgan MD (2003). Nutritional enhancement of exercise performance in chronic obstructive pulmonary disease: a randomised controlled trial. *Thorax* **58**: 745–751.

Suissa S (2004). Inhaled steroids and mortality in COPD: bias from unaccounted immortal time. *Eur Respir J* **23**: 391–395.

Suissa S (2006). Statistical treatment of exacerbations in therapeutic trials of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* **173**: 842–846.

Sutherland ER, Allmers H, Ayas NT, Venn AJ, Martin RJ (2003). Inhaled corticosteroids reduce the progression of airflow limitation in chronic obstructive pulmonary disease: a meta-analysis. *Thorax* **58**: 937–941.

Swallow EB, Reyes D, Hopkinson NS, Man WD, Porcher R, Cetti EJ *et al.* (2007). Quadriceps strength predicts mortality in patients with moderate to severe chronic obstructive pulmonary disease. *Thorax* **62**: 115–120.

Tashkin D, Kanner R, Bailey W, Buist S, Anderson P, Nides M *et al.* (2001). Smoking cessation in patients with chronic obstructive pulmonary disease: a double-blind, placebo-controlled, randomised trial. *Lancet* **357**: 1571–1575.

Turner MC, Chen Y, Krewski D, Calle EE, Thun MJ (2007). Chronic obstructive pulmonary disease is associated with lung cancer mortality in a prospective study of never smokers. *Am J Respir Crit Care Med* **176**: 285–290.

Vestbo J, Sorensen T, Lange P, Brix A, Torre P, Viskum K (1999). Long-term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* **353**: 1819–1823.

Walker PP, Burnett A, Flavahan PW, Calverley PM (2008). Lower limb activity and its determinants in chronic obstructive pulmonary disease. *Thorax* **63**: 683–689.

Wedzicha JA, Calverley PM, Seemungal TA, Hagan G, Ansari Z, Stockley RA (2008). The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. *Am J Respir Crit Care Med* **177**: 19–26.

Yin P, Jiang CQ, Cheng KK, Lam TH, Lam KH, Miller MR *et al.* (2007). Passive smoking exposure and risk of COPD among adults in China: the Guangzhou Biobank Cohort Study. *Lancet* **370**: 751–757.