Background Paper 6.13
Chronic Obstructive Pulmonary Disease (COPD)

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What’s new since 2004?

The fact that in 2013, available treatments for chronic obstructive pulmonary disease (COPD) are mainly palliative and there are no therapies available that halt the decline in lung function or the progressive destruction of the airways associated with the disease, suggests that not much has changed since the original Priority Medicines Report. While, our knowledge of COPD has grown over the past few years many questions still remain.1, 2

- One of the biggest advances in COPD is greater understanding of the disease burden in different countries and cultures. It is important to establish how important COPD is, particularly in view of the disease’s consistent under-diagnosis at sites where it has been investigated.

- There are striking differences between COPD prevalence in different countries even when using identical detection methods.

- We do not know if undiagnosed COPD is clinically important and a predictor of bad outcomes.

- We understand more about the systemic nature of COPD disease, as some of the most important effects arise in organs outside the respiratory system.

- COPD is a disease of ageing. Furthermore, if every smoker in the world were to stop smoking today, the rates of COPD would probably continue to increase for the next 20 years.

- Since 2004, large-scale, integrated research efforts, both national and international are contributing to knowledge about COPD risk factors and epidemiology (e.g. COPD Biomarkers Qualification Consortium (CBQC) (See Section 8.3.2), SPIROMICS (See Section 8.3.2), COPDGene (See Section 8.3.2), COPDMAP and IMI PROactive (See Section 8.3.1)).

- The heterogeneity of COPD and the lack of validated (or qualified) drug development tools still limits the ability to assess novel medicines that may impact disease progression or extra-pulmonary manifestations of COPD. This process requires large (over 10 000 patients and 3-4 years in duration), but if efforts of large-scale initiatives such as those listed above are successful, we may be able to conduct stratified medicine trials, selecting patients at risk for poor outcomes.

- Major pharmaceutical companies have been conservative with their business model and have invested in management of currently marketed medicines and developing next-generation versions of well-established classes. As a result of this bias towards low risk efforts in COPD, genuinely novel pipeline medicines for COPD are still relatively scarce among such companies, although the situation is improving.
**Executive Summary**

Chronic obstructive pulmonary disease (COPD) is a disease state characterized by airflow limitation that is not fully reversible. COPD is the fourth leading cause of death worldwide and it is largely preventable. The main cause in developed countries is exposure to tobacco smoke. Other preventable causes include exposure to indoor and outdoor air pollution, such as occupational exposure (firefighters, farm workers) and the burning of biomass fuel for cooking and heating which impacts many women in Africa, China, and India.

In 2010, COPD was estimated to account for 2.7% of the disease burden and 3.2% of deaths in Europe, and for 3.1% of the global disease burden and 5.5% of deaths worldwide. Worldwide prevalence of ‘moderate’ COPD estimated by the Global Initiative on Obstructive Lung Disease (GOLD) in adults aged 40 years and older is 9–10%. Stage III COPD (generally considered as “severe”) drives most of the costs of COPD. Its prevalence across 12 sites around the globe ranged from 0.8% (Hannover, Germany) to 6.7% (Cape Town, South Africa) The Burden of Obstructive Lung Disease initiative used standardized methods to investigate the prevalence of COPD around the world and showed important differences between countries. Prevalence ranged from 9% in Reykjavik, Iceland to 22% in Cape Town, South Africa, for men, and from 4% in Hannover, Germany to 17% in Cape Town for women.

Chronic obstructive pulmonary disease is associated with major morbidity and mortality such as cardiovascular disease, muscle wasting, type 2 diabetes, and asthma. Smoking cessation will probably have the most important effects on COPD as a public health problem in Europe and the world as it slows disease progression and lowers mortality.

None of the existing medications for COPD has been shown to modify the long-term disease progression such as decline in lung function in many patients or worsening of health status. Therefore, pharmacotherapy for COPD is used to alleviate symptoms and/or prevent complications. Inhaled bronchodilators are the mainstay treatment for COPD. Two large-scale, long-term, landmark studies have confirmed the efficacy of a fixed dose combination of a long-acting β2 agonist (salmeterol) and inhaled corticosteroid (fluticasone) and a long-acting anticholinergic agent (tiotropium).

Substantial unmet needs remain in COPD preventing the progression of COPD. Drug development for COPD is difficult owing to the chronic and slowly progressive nature of the disease. Not a single new therapy has come from information on pathogenic inflammatory processes. What is needed are surrogate markers of inflammation that may predict the clinical usefulness of new management and prevention strategies for COPD, new clinical end points to assess the impact of different COPD interventions and standardized methods for tracking trends in COPD prevalence, morbidity, and mortality over time.

New medicines for the treatment of COPD are greatly needed and there has been an enormous effort now invested by the pharmaceutical industry to find such treatments. While preventing and quitting smoking is the obvious preferred approach, this has proved to be very difficult. Not all COPD is due to cigarette smoking, especially in low- and middle-income countries (LMIC).
1. **Introduction**

Chronic obstructive pulmonary disease (COPD) is a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases. The pathology of COPD includes emphysema and chronic bronchitis, although only one of these may be present in some people with COPD. Emphysema is the abnormal permanent enlargement of the air spaces distal to the terminal bronchioles, accompanied by destruction of their walls, and without obvious fibrosis. Chronic bronchitis is chronic cough or mucous production for at least three months in at least two successive years when other causes of chronic cough have been excluded.

Chronic obstructive pulmonary disease progresses over many decades and tends to present in advanced stages, thus most treated patients are middle aged or elderly. Chronic obstructive pulmonary disease is the fourth leading cause of death worldwide resulting in more than 2.7 million deaths in 2000. The United States National Heart, Lung, and Blood Institute has estimated that it has resulted in a US$ 32.1 billion loss to the USA economy in direct and indirect costs in 2003, with direct costs totaling US$ 18 billion. By 2020, COPD is expected to become the third most common cause of death.

Yet despite the high disease burden and financial costs incurred, efforts to address the problem of chronic respiratory diseases, and COPD in particular, have never received adequate funding in any country, whether for research, prevention, or clinical services.

Chronic obstructive pulmonary disease is largely preventable. The main cause in developed countries is exposure to tobacco smoke. In developed countries, 85% to 90% of people with COPD have smoked at some point. Other preventable causes include exposure to indoor and outdoor air pollution, such as occupational exposure (firefighters, farm workers) and the burning of biomass fuel for cooking and heating which impacts many women in Africa, China, and India.

The disease is, unfortunately, relatively common in lifelong non-smokers that have been exposed to these passive conditions. Other proposed causes include allergy, bronchial hyper-responsiveness, and genetic predisposition (the most well-characterized is hereditary A1AT deficiency).

Current therapies address the symptoms only and they range from bronchodilators, anti-inflammatory agents (e.g. corticosteroids, anti-inflammatories, and PDE4 inhibitors) to oxygen. There are no effective cures and there is no single diagnostic test for COPD. Making a diagnosis relies on clinical judgment based on a combination of history, physical examination, and confirmation of the presence of airflow obstruction using lung function testing (spirometry).

The public health situation with regard to COPD is, in broad outline, similar to other preventable chronic conditions such as alcoholic liver disease (See updated Chapter 6.14) where the relatively limited success of primary and secondary prevention of alcohol
consumption is coupled with the notion that alcohol-induced liver disease is largely a self-inflicted disease.

Smoking cessation will probably have the most important effects on COPD as a public health problem in Europe and the world. Indeed, patients who stop smoking experience less decline in lung function over time. Nonetheless, this document is a summary of pharmacological interventions and gaps to treat existing COPD from that viewpoint.

2. What Are the Epidemiological Trends for Europe and the World?

Chronic obstructive pulmonary disease is associated with major morbidity and mortality. A number of co-morbid conditions not directly related to COPD are included in this such as cardiovascular disease, muscle wasting, type 2 diabetes, and asthma. Although the association between COPD and its systemic comorbidities is not fully understood, it may involve the persistent, low-grade pulmonary, and systemic inflammation seen in COPD. This systemic inflammation is independent of cigarette smoking status and persists after smoking cessation.

One of the most frequently reported co-morbidities of COPD is asthma. Both COPD and asthma are major chronic obstructive airway diseases that involve underlying airway inflammation, but the type of inflammatory process differs; the airway inflammation in asthma is typically reversible and is mediated by white blood cells called eosinophils, whereas COPD is characterized by inflammation mediation by white blood cells called neutrophils that does not respond well to standard asthma therapies.

By 2012, COPD drug costs are expected to reach almost 6 billion dollars per year in the USA, Japan, and part of Western Europe alone. This estimate excludes many large and populous areas, such as India and China, where COPD is becoming an increasingly recognized and prevalent condition, both due to smoking and other sources of air pollution.

It is likely that the impact of COPD has been under-estimated due to a lack of accurate epidemiologic data from some countries, misdiagnosis, and inconsistent use of the International Classification of Diseases (ICD) codes when reporting causes of death in patients with COPD. Particularly worrying is the marked increase in deaths (in most, but not all countries) due to COPD over the past couple of decades, a trend that is predicted to continue. Another cause for concern is the dramatic rise in COPD mortality seen in women in many countries. In addition to the considerable mortality and morbidity burden of COPD, this condition also incurs significant financial costs associated with the care of patients and lost productivity of patients and caretakers.

- Improved treatment of COPD, and the ability of a therapeutic intervention to improve survival, therefore represents an important goal.

Currently, smoking cessation is the single most effective intervention to improve outcomes in patients with COPD; however, even in the best programs less than one-third of patients sustain abstinence, and even nonsmokers will usually continue to experience dyspnea and
other symptoms as airflow limitation persists. A recent structured and comprehensive literature review identified published data on the prevalence, incidence, and mortality in COPD, and/or trends in those data.\textsuperscript{12}

### 2.1 Prevalence

There is a wealth of data on the prevalence of COPD in eleven countries (Australia, Canada, France, Germany, Italy, Japan, the Netherlands, Spain, Sweden, the UK, and the USA).\textsuperscript{12} When all studies were taken into account, prevalence estimates were remarkably wide, ranging from 0.2\%–37\%, which was in line with earlier reviews (2.1\%–26.1\%).\textsuperscript{12}

Worldwide prevalence of ‘moderate’ COPD estimated by the Global Initiative on Obstructive Lung Disease (GOLD) in adults aged 40 years and older is 9–10\%.\textsuperscript{12} Stage III COPD (generally considered as “severe”) drives most of the costs of COPD. Its prevalence across 12 sites around the globe ranged from 0.8\% (Hannover, Germany) to 6.7\% (Cape Town, South Africa).\textsuperscript{13}

The Burden of Obstructive Lung Disease initiative used standardized methods to investigate the prevalence of COPD around the world and showed important differences between countries.\textsuperscript{13} Prevalence ranged from 9\% in Reykjavik, Iceland to 22\% in Cape Town, South Africa, for men, and from 4\% in Hannover, Germany to 17\% in Cape Town for women.

COPD clearly increases with age in both genders, with few exceptions, as patients with earlier disease often go undiagnosed.

Younger ages see great variation in reported prevalence as well as gender differences in which men usually show higher prevalence than women. Prevalence increases dramatically with age and the gender differences tend to remain, except in China, South Africa, Iceland.
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Figure 6.13.1 and Figure 6.13.2. Estimated population prevalence of GOLD stage II or higher COPD, separated by age

### Men

![Graph showing estimated population prevalence of GOLD stage II or higher COPD in men, separated by age and location.](image_url)

### Women

![Graph showing estimated population prevalence of GOLD stage II or higher COPD in women, separated by age and location.](image_url)
Source: Data in Annex 6.13.1, adapted from reference\textsuperscript{13}
2.2 Mortality

There is no doubt variability in this metric due, in part, owing to the variation in the numbers of countries analyzed. For instance, mortality within the overall population (range: 3–111 per 100,000) should be compared with a European-based study (7.2–36.1 per 100,000). The latter found a greater mortality rate in European men compared with European women. The Rycroft review also reported that, although COPD mortality rates have increased over time (starting from the 1970s), rates have declined within the last decades, which suggests improvements in COPD management.

The lowest and highest mortality estimates were from Japan and the USA, respectively, which were not captured in the European-focused literature review noted above. With regard to the USA, age-adjusted mortality for COPD in the USA doubled from 1970 to 2002, although in other developed countries there are suggestions of a decline in the incidence and prevalence. These declines are related to decreases in the prevalence of smoking and reductions in air pollutants. In developing countries prevalence has risen strikingly, owing to increased smoking rates and reductions in other causes of death, particularly from severe infections.

The difference in these trends may be explained by trends in smoking prevalence in the countries of interest. Several countries had a clear difference in COPD mortality trends that was observed between men and women (i.e. Australia, France, and the USA). These countries all showed an overall decline in smoking rates with the greatest prevalence change in men.

2.3 Under-diagnosis and under-treatment of COPD

Another important feature in the epidemiology of COPD is the high risk of underdiagnoses. Sixty to 85% of patients, mainly with mild to moderate disease, are thought to remain undiagnosed. In a survey in Spain, 10% of adults aged 40–80 years had COPD, but only 27% of them had been previously diagnosed.

A recent study in the USA demonstrated a major impact of COPD on the population of USA war veterans (Veterans Administration (VA)). Almost 10% of patients in the south-eastern United States seen in the VA health care system had COPD. This prevalence is generally comparable to estimates from the National Heart Lung and Blood Institute (NHLBI). Perhaps the most striking finding was the apparent under-treatment of the COPD population in the VA system. Approximately 40% of these VA patients were not receiving any of the medications recommended in global treatment guidelines at baseline.

The most common respiratory medication class prescribed for VA patients with COPD was short-acting beta-2 agonists, which according to treatment guidelines are to be used as rescue medications and not as maintenance treatment. Maintenance treatment with guidelines-recommended long-acting bronchodilators was prescribed in the minority of VA patients. These findings are consistent with results of studies from Canada, Japan, and Europe, using non-veteran patients.

Clearly, there are difficulties with burden of diseases measures of COPD. For example, the estimated COPD death rate in Japan of 4.4/100,000 is nearly 30 times lower than that in China.
Findings of an epidemiological study of COPD in Japan, however, showed that 16.4% of men and 5.0% of women aged 40 years and older had disease of GOLD stage I or higher, which is similar to the 15.3% of men and 7.6% of women with a similar COPD stage in a Chinese study. The difference between Japan and China in COPD mortality rates versus the similarity in prevalence suggests that other factors (e.g. stigma of a diagnosis of COPD) might affect how disease is diagnosed and cause of death is attributed between countries.

2.4 Co-morbidities

Patients with COPD typically have comorbid conditions, such as lung cancer, cardiovascular disease (e.g. ischemic heart disease, depression, muscle wasting, reduced fat-free mass, osteopenia, and chronic infections). One explanation for this is that tobacco use drives disease in multiple organs. These disorders contribute to a high disease burden and early mortality in patients with COPD. Deaths in individuals with COPD are frequently attributed to a cause other than COPD. For example, in a large prospective cohort from the USA of deaths in people with advanced COPD, 31.5% were recorded as a respiratory cause, 23.9% were due to lung cancer, 13.0% were due to cardiovascular disease, and 31.5% were from other causes.1

Several studies suggest that cardiovascular diseases are more frequent in COPD patients than in the general population and may represent a burden greater than that of lung disease itself. In addition, among COPD comorbidities, depression deserves particular attention. Chronic obstructive pulmonary disease (especially at severe levels) leads to impairments in activities of daily living, social, and psychological functioning and recreational activities. Depression has been found to occur in 7%–42% of COPD patients which is up to four times more frequent than in subjects without COPD.19

Skeletal muscle dysfunction is a frequent and clinically relevant systemic manifestation of COPD that has been associated with morbidity and mortality independently from the severity of lung function impairment in COPD. In spite of the unequivocal benefit of exercise training in the context of pulmonary rehabilitation at reducing disability and healthcare utilization and improving survival, there remains an unmet need for therapy,

- These observations highlight the fragmentary nature of available information, and at the same time the importance of studying COPD comprehensively, considering often-associated concomitant conditions and quantifying the burden of illness that these conditions cause in this population.
3. **What is the Control Strategy? Is There an Effective Package of Control Methods Assembled into a “Control Strategy” for Most Epidemiological Settings?**

The overall approach to managing stable COPD is characterized by a stepwise increase in treatment, depending on the severity of the disease. These treatments fall into three broad areas: prevention of disease progression, management of stable disease, and management of exacerbations.

- Given that there is no cure for the underlying inflammation of COPD, we can say that there is a pharmaceutical “gap”.
- Formerly, the pharmaceutical industry relied on variations of existing palliatives, but there is now a major effort generally by the industry to change the way novel medicines are studied and approved. Still, third party payers are focused on COPD as a whole and less on subsets of patients based on unmet need.

### 3.1 Stable COPD

The most recent guideline (December 2011) for treatment is the GOLD strategy\(^\text{20}\). This replaces a previous guideline\(^\text{21}\) as it considered a more personalized approach including history of exacerbations and comorbidities.

For all patients, smoking cessation, reduction in exposure to environmental and occupational risk factors, and yearly influenza vaccinations are recommended. The first step is usually smoking cessation. **This intervention slows disease progression and lowers mortality.**

Inhaled bronchodilators are the mainstay treatment for COPD (Appendix 6.13.1). For very severe disease (GOLD stage 4) surgical options include lung transplantation and lung-volume reduction is an option if quality of life is unacceptably low. Respiratory rehabilitation is usually considered at all stages in patients with muscle weakness, deconditioning, and poor quality of life. This treatment is aimed at improving quality of life and exercise capacity. Oxygen supplementation for those with chronic hypoxemia is very important and may reduce mortality. Treatment for associated comorbidities is also vital.

Two large-scale, long-term, landmark studies have confirmed the efficacy of a fixed dose combination of a long-acting β2 agonist (salmeterol) and inhaled corticosteroid (fluticasone) and a long-acting anticholinergic agent (tiotropium).\(^\text{22}\)

None of the existing medications for COPD has been shown to modify the long-term disease progression such as decline in lung function in many patients or worsening of health status. Therefore, pharmacotherapy for COPD is used to alleviate symptoms and/or prevent complications. While disease prevention is the ultimate goal, once COPD has been diagnosed, effective management should be aimed at the following goals:

- Prevent disease progression: airflow obstruction, emphysema, extrapulmonary disease
- Relieve symptoms of dyspnea, cough and sputum
- Improve the ability to perform activities of daily living (exercise tolerance)
Update on 2004 Background Paper, BP 6.13 COPD

- Improve health status
- Prevent and treat exacerbations
- Reduce mortality

Only two interventions have been shown to increase survival of smokers who develop chronic obstructive pulmonary disease. The first is stopping smoking, which is beneficial at all stages of the disease. The second is long term oxygen therapy, which increases the life expectancy of patients with chronic respiratory failure. In the TORCH study, the reduction in mortality showed a trend in favor of the salmeterol/fluticasone combination.

3.2 Exacerbations of Symptoms in COPD

Acute exacerbations of respiratory symptoms requiring medical intervention are important clinical events in COPD. Common causes of an exacerbation are viral upper respiratory infections, and lower respiratory infections (acute bronchitis, pneumonia).

Inhaled steroids (ICS)/long-acting bronchodilator combinations and the long-acting antimuscarinic tiotropium all improve health status and exacerbation rates and may have an effect on mortality but perhaps only with prolonged use. Chronic antibiotic use (e.g. erythromycin) has been shown to decrease the rate of COPD exacerbations. Indacaterol is an ultra-long-acting beta-adrenoceptor agonist and was approved by the European Medicines Agency (EMA) under the trade name Onbrez® on November 30, 2009 and by the Food and Drug Administration (FDA) under the trade name Arcapta Neohaler® on July 1, 2011.

3.3 Genotypic risk factors:

Severe α1 antitrypsin (α1AT) deficiency is a proven genetic risk factor for COPD yet increasing evidence suggests that other genetic determinants also exist. The presence of genetic determinants of lung function that do not depend on prior smoking exposure has been suggested by previous studies of heritability and has been clearly proven in 2010 using a genetic study of 2.5 million sites across the human genome involving samples from 20 000 people across the world.

Smoking is the major risk factor for both COPD and lung cancer. Because both COPD and lung cancer are inheritable, the genetic characteristics conferring this dual susceptibility might overlap. Recently, eleven genome-wide association studies (GWAS) have reported several susceptibility loci for COPD and lung cancer. All these studies have revealed that the single nucleotide polymorphisms (SNPs) located in nicotinic acetylcholine receptor genes (CHRNA3, CHRN4, CHRNA5) mapped to chromosome 15 q25 are shared by the two diseases. To be fair, this particular shared genetic etiology may simply be due to nicotine-dependence, because these SNPs are also associated with smoking behavior.

- In the past it has been difficult to develop new treatments because the molecular pathways that affect the health of the lung are not completely understood. It is hoped genetic studies will lead to new pathways that could in the future be targeted.
4. What is Known of the Affordability, Feasibility, and Sustainability of the Control Strategy?

Chronic obstructive pulmonary disease treatment, particularly in the elderly, has been expensive because of the high rate and length of hospital admissions in these patients.\textsuperscript{27, 28} It must also be noted that current therapies, however, are limited in important ways.

The bronchodilators that were developed originally for the treatment of asthma, exploit the small degrees of smooth muscle tone that are present in COPD patients. By inducing smooth muscle relaxation, airflow can be improved, but only very modestly. These small gains, perhaps unsurprisingly, can be exceedingly meaningful for some COPD patients.

Unlike asthma, however, COPD patients are often given anticholinergic bronchodilators in addition to beta-2 agonists with benefit. Combinations of long-acting beta-2 agonist and anticholinergic bronchodilators provide greater bronchodilation than either agent alone. Fixed combination products containing a long acting beta-2 agonist (LABA) and an ICS are superior to either component alone for lung function. The most benefit for lung function is obtained when patients take triple therapy (e.g. a LAMA, LABA, and ICS), a strategy often used in the most severe patients.

While current therapies can clearly be beneficial in treating the symptoms and exacerbations of COPD, new treatments are needed. In particular, the development of novel medicines that ameliorate the inflammatory and abnormal airway secretory responses initiated in response to chronic irritation from inhaled smoke - processes which are often resistant to inhaled steroids - may provide useful steps toward reduction of the ongoing destruction of the lung tissue and the progressive, relentless deterioration in pulmonary function that culminates in respiratory failure and death. This is the “holy grail” of therapy in patients with COPD.

4.1 Economic Burden

Chronic obstructive pulmonary disease is a progressive and debilitating disease, in its severe form, is not very responsive to therapy and its symptoms limit exercise tolerance and impair patients’ ability to work.\textsuperscript{29}

The European Lung White Book (2003) estimated that the total annual cost of COPD in Europe was €38.7 billion (including €4.7 billion for ambulatory care, €2.7 billion for medicines, and €2.9 billion for in-patient care). As these data exclude mortality costs, the actual cost incurred by COPD may be much higher.\textsuperscript{6}

4.1.1 Global estimates of costs

Globally, costs vary between countries that have reported them, although more severe disease consistently incurs more costs than less severe disease. One means of measuring costs is to ascertain how expensive a specific intervention would be per quality-adjusted life year of improvement. Using this approach, WHO estimated in 2001 that costs per quality-adjusted life year (QALY) for COPD range from US$ 6 700–8 900 for inhaled ipratropium to US$ 13 400 for inhaled corticosteroids to US$ 238 200 for lung transplantation.\textsuperscript{30} These estimates need updating.
More recent estimates put, for instance, the cost per QALY for lung transplantation to be closer to US$ 80 000 \(^{31}\) and the cost/QALY for inhaled corticosteroids to be between US$ 5 000-10 000. \(^{32}\) Although one would expect smoking cessation to also be very cost effective, this invention has not been assessed with respect to quality-adjusted life years for COPD.\(^{1,7}\)

### 4.1.2 United Kingdom

In the UK, early estimates of the total costs to the National Health Service (NHS) for COPD are somewhere between £486 million (£719 million)\(^{33}\) and £848 million (£1 255 million)\(^{33}\) per year. Additionally, societal costs, most notably productivity costs (costs arising from loss of income through inability or absence from work), pushes total costs for COPD up to £982 million (£1 453 million) per year.\(^{33}\) This translates to a per patient cost of between £781(£1 156) and £1 154 (£1 708) per year (£1 639 (£2 425) when including societal costs.

All these estimates are over 10 years old. A recent 2010 modeling study (Appendix 6.13.2) estimates that, in the UK alone, the economic burden is £1.2 billion per annum. This includes not only direct healthcare costs, but factors such as lost income tax, payment of state benefits and productivity loss due to COPD. These calculations are based on the current age of retirement — if this is increased then the economic impact will also rise. More specifically, the annual healthcare costs due to COPD in patients aged 45–64 years are £277.7 million (or €315.7 million / $440.1 based on 2009 values) The annual costs of lost productivity due to early retirement among people with COPD aged 45–64 years amounted to £522.9 million (or €592.6 million / $828.5 million), representing 21% of the productivity that would have been generated by these people if they had not retired early.

The major drivers of this burden are disease severity and exacerbations. These are discussed below in Section 4.1.4.

### 4.1.3 United States

Studies evaluating COPD costs have generated widely variable estimates. A review in 2006 summarized and critically compared recent estimates of the annual national and per-patient costs of COPD in the USA\(^{34}\) Few papers reported indirect costs of COPD (lost work and productivity). The National Heart, Lung, and Blood Institute (NHLBI) provided the single current estimate of the total (direct plus indirect) annual cost of COPD to the USA, $38.8 billion in 2005 dollars. More than half of this cost ($21.8 billion) was direct. For per-patient direct costs (in US$ 2005), studies using recent data yield attributable cost estimates (costs deemed to be related to COPD) in the range of $2 700-$5 900 annually, and excess cost estimates (total costs incurred by COPD patients minus total costs incurred by non-COPD patients) in the range of $6 100-$6 600 annually. Hospitalization is a major cost driver in COPD management in various health care systems with hospital care projected to account for 45% of direct COPD costs in the USA in 2010.\(^{34}\)

However, published data appear to be lacking regarding costs for USA commercially insured patients and USA costs according to COPD severity. One study of managed care patients in the USA found mean annual COPD-related health care costs (in US$ 2008) ranging from $2 003 ($3 238) to $43 461 ($76 159) per patient.\(^{35}\) Medical costs comprised 96% of health care costs for an intensive care unit (ICU) cohort. Adjusted mean episode-level costs were $305 ($310) for an outpatient visit, $274 ($336) for an urgent outpatient visit, $327 ($65) for an
emergency department visit, $9 745 ($2 968) for a standard admission, and $33 440 for an ICU stay.

In 2010, COPD accounted for $49.9 billion in health care expenditures in the United States alone ($29.5 billion in direct health care expenditures, $8.0 billion in indirect morbidity costs, and $12.4 billion in indirect mortality costs.

4.1.4 Drivers of cost: Severity and Exacerbations

Costs increase substantially as disease severity moves from moderate to severe. As lung function (e.g. FEV1) declines, a general shift from outpatient care to hospitalization, an increase in the use of oxygen therapy, and a subsequent increase in total costs, especially in the most advanced stages of the disease, has been shown to occur.

Exacerbations are the leading driver of cost in COPD. A serious exacerbation will lead to hospitalization; indeed, an exacerbation is the main reason why a COPD patient would attend hospital. The cost of exacerbations has been found to increase in line with the severity of exacerbations; a Swedish study reports: €13 for a mild, €38 for mild/moderate, €225 moderate, and € 2 326 for a severe exacerbation. Exacerbations account for between 35–40% of total health care costs for COPD patients. Treatment which acts to reduce or prevent disease progression and or an exacerbation (particularly severe exacerbations) will have a direct effect on the total cost for COPD.

4.1.5 Productivity costs

Productivity costs are generally regarded as the cost of time off work due to illness. Productivity costs for COPD represent a substantial burden on society as COPD is a major cause of absenteeism from work. Within the 15 original EU member states, COPD is estimated to annually account for 41 300 lost work days per 100 000 people and productivity losses of around 28.5 billion per year.

5. Why Does the Disease Burden Persist?

- There is presently no cure for COPD. The condition is not currently well controlled by available medicines, which are unable to fully resolve inflammation and to prevent lung tissue destruction, as well as the associated progressive decline in pulmonary function. Novel and more effective therapies are urgently needed.

Most significantly, its etiology is confounded with the culture of tobacco, smoking, and poverty. The prevalence of chronic obstructive pulmonary disease, indeed for many chronic diseases, is greatest in socio-economically deprived people. The reasons for its persistence may be more related to health policy/health system dysfunctions than a lack of treatment options.

- Chronic respiratory diseases and COPD in particular have never, in any area of the world, been accorded a priority relative to their extent and impact. No political jurisdiction (rich or poor) proportionally commits resources to chronic respiratory
diseases equivalent to the burden they represent in the community, whether for research, prevention, or clinical services.

It was only in 2005, that the World Health Organization (WHO) released a report highlighting the high burden of chronic diseases particularly in developing countries and the need for urgent action in the prevention and control of chronic diseases including chronic respiratory diseases (See Appendix 6.13.3). The reasons for this neglect are unclear. Several possible explanations can be offered.

These diseases have traditionally been stigmatized. It has been virtually impossible to mobilize either patients or society to address them as has been done for HIV/AIDS. With conditions related to tobacco smoke exposure (lung cancer and chronic obstructive pulmonary disease) there has been a ‘blame the victim’ approach which promotes stigmatization.

Some guidelines have been published for the management of COPD in developing countries. A standard case management approach for COPD for Asia and Africa has been proposed. Notwithstanding, such guidelines are usually developed by professional societies and/or specialists and rarely involve service providers at the primary care level. Additional bottlenecks in developing countries are: the low priority accorded to chronic diseases as compared with infectious diseases; lack of organization of follow-up; cultural barriers; poor education of health workers; lack of spirometry in low-income countries; and lack of access to, and the high cost of necessary medicines.

5.1 COPD and the “never smoker”

Lambrecht et al. analyzed data from 14 countries that participated in the international, population-based Burden of Obstructive Lung Disease (BOLD) study. Participants were aged ≥ 40 years. Among 4,291 never smokers, 6.6% met criteria for mild (GOLD stage I) COPD and 5.6% (n=240) met criteria for moderate to very severe (GOLD stage II+) COPD.

Although never smokers were less likely to have COPD and had less severe COPD than ever smokers, never smokers nonetheless comprised 23.3% (240/1,031) of those classified with GOLD stage II+ COPD. This multicenter international study confirmed previous evidence that never smokers comprise a substantial proportion of individuals with COPD.

Among younger ages, the study showed that exposure to indoor air pollution was the most important cause for COPD because of exposure to biomass fuel since childhood. Compared to 1.1 billion smokers more than three billion people (50% of the global population) use biomass fuels (wood, crop residue, and cow dung cakes) for cooking and heating. In India alone, 75% of the homes use biomass fuel, exposing over 700 million people to high levels of indoor air pollution. Women and young children are the most vulnerable group that are affected due to this exposure.
6. What Can Be Learned from Past/Current Research into Pharmaceutical Interventions for this Condition?

The key points below were extracted from the summary provided by BMJ Clinical Evidence:\(^2\)

- The main risk factor for the development and deterioration of chronic obstructive pulmonary disease (COPD) is still smoking.

Inhaled anticholinergics and beta-2 agonists improve lung function and symptoms and reduce exacerbations in stable COPD compared with placebo.

- It is unclear whether inhaled anticholinergics or inhaled beta-2 agonists are the more consistently effective drug class in the treatment of COPD.
- Short-acting anticholinergics seem to be associated with a smaller improvement in quality of life compared with beta-2 agonists.
- Long-acting inhaled anticholinergics may improve lung function more when compared with long-acting beta-2 agonists.
- Combined treatment with inhaled anticholinergics plus beta-2 agonists may improve symptoms and lung function and reduce exacerbations compared with either treatment alone, although long-term effects are unknown.

Inhaled corticosteroids reduce exacerbations in COPD and reduce decline in lung function, but the beneficial effects are small.

- Oral corticosteroids may improve short-term lung function, but have serious adverse effects.
- Combined inhaled corticosteroids plus long-acting beta-2 agonists improve lung function, symptoms, and health-related quality of life, and reduce exacerbations compared with placebo, and may be more effective than either treatment alone.

Long-term domiciliary oxygen treatment may improve survival in people with severe daytime hypoxaemia.

Theophylline may improve lung function compared with placebo, but adverse effects limit its usefulness in stable COPD.

We do not know whether mucolytic medicines, prophylactic antibiotics, or alpha\(_1\) antitrypsin improve outcomes in people with COPD compared with placebo.\(^2\)

Although not within the ambit of this Background document, inasmuch as it is a non-pharmacologic treatment, we briefly note that pulmonary rehabilitation using physical activity has been shown to be beneficial.

One of the main challenges in developing new therapeutic agents for the treatment or prevention of acute exacerbations of COPD is that their potential success cannot be entirely known until the investigational therapies enter relatively large Phase II studies, assessing clinical outcome over a three to six month period or longer.\(^2\)
6.1 Overview of the existing Medications

Pharmacologic therapy is used to prevent and control symptoms, reduce the frequency and severity of exacerbations, improve health status, and improve exercise tolerance. None of the existing medications for COPD has been shown to conclusively modify the long-term decline in lung function that is the hallmark of this disease. The medications are presented in the order in which they would normally be introduced in patient care, based on the level of disease severity.

6.1.1 Bronchodilators

Medications that increase lung function by altering airway smooth muscle tone, are termed bronchodilators, since the improvements in expiratory flow reflect widening of the airways rather than changes in lung elasticity. Regular bronchodilation with medicines that act primarily on airway smooth muscle does not modify the decline of function in mild COPD and, by inference, the prognosis of the disease. Bronchodilator medications are central to the symptomatic management of COPD. The side effects of bronchodilator therapy are pharmacologically predictable. However, COPD patients tend to be older than asthma patients and more likely to have comorbidities, so their risk of developing side effects is greater.

B2-agonists

Long-acting B2-agonists improve lung function, improve health status, and reduce exacerbations. Oral therapy is slower in onset and has more side effects than inhaled treatment.

Anticholinergics

Anticholinergic medications are a class of drugs that have long been used to improve symptomatology of patients with COPD. An inhaled anticholinergic medication, tiotropium bromide (Boehringer Ingelheim, Ingelheim, Germany), is now being used in this patient population. This medication appears to be more effective in treating patients with COPD compared with older anticholinergics.

Methylxanthines

Controversy remains about the exact effects of xanthine derivatives. Data on duration of action for conventional or even slow-release xanthine preparations are limited in COPD. Theophylline is effective in COPD but toxicity is dose related. Unlike the other bronchodilator classes, xanthine derivatives may involve a risk of overdose.

6.1.2 Glucocorticosteroids (GCs)

Glucocorticosteroids are not effective at controlling the chronic inflammatory response in COPD. To date, there are no effective treatments to control this persistent inflammatory response and the associated decline of lung function of COPD. This is largely due to a lack of understanding of the nature of the inflammatory response in COPD and the impact of key underlying factors such as oxidative stress on this inflammatory response.
Oral glucocorticosteroids.

Many existing COPD guidelines recommend the use of a short course (two weeks) of oral glucocorticosteroids to identify COPD patients who might benefit from long-term treatment with oral or inhaled glucocorticosteroids. A short course of oral glucocorticosteroids is a poor predictor of the long-term response to inhaled glucocorticosteroids in COPD.

Oral glucocorticosteroids - long-term.

Based on the lack of evidence of benefit, and the large body of evidence on side effects, long-term treatment with oral glucocorticosteroids is not recommended.\(^2\)

Inhaled glucocorticosteroids.

Although both inhaled and oral GCs are effective at controlling inflammatory lung diseases such as asthma, their effectiveness is substantially less in COPD; therefore, their contribution to the management of stable COPD is limited.\(^5^3\)

Although results published from the Towards a Revolution in COPD Health (TORCH) study of patients with COPD indicated that regular use of inhaled GCs may decrease the rate of decline of lung function, the majority of studies have concluded that the use of regular inhaled GCs has no impact on the long-term progressive decline in lung function.\(^2\)

Combination therapy (inhaled corticosteroids + long acting beta agonists).

In clinical trials with COPD, combined budesonide–formoterol administered via a dry powder inhaler has proven more effective in improving lung function and reducing exacerbations when compared with the same dose of budesonide or formoterol given alone. Budesonide–formoterol combination therapy is also safer and tolerated better than the same dose of budesonide or formoterol given alone.\(^5^4\)

6.1.3 Phosphodiesterase-4 inhibitors

Phosphodiesterases (PDEs) are important modulators of inflammation and wound healing. In this capacity, specific targeting of PDEs for the treatment of many diseases, including COPD, has been investigated. PDE4 modulates the inflammatory response of the lung, and inhibition of PDE4 may be a novel, COPD-specific approach toward more effective treatment strategies.\(^5^9\)

Roflumilast, the first new class of treatment for COPD in more than a decade, is a selective long-acting phosphodiesterase 4 (PDE4) enzyme inhibitor recently approved for treatment of patients with severe COPD (Daxas® was approved in the June 2010 for severe associated with history of exacerbations and chronic bronchitis).\(^5^6\) In March 2011, Daliresp® gained FDA approval for reducing COPD exacerbations.\(^5^7\)

Roflumilast, an oral specific phosphodiesterase 4 inhibitor was associated with a 17% reduction in the frequency of exacerbations in patients with GOLD stage 3–4 COPD and history of exacerbations, cough, and sputum changes.\(^5^5\) In June 2010, roflumilast (Daxas®, Daliresp®) was approved in the EU for severe COPD associated with chronic bronchitis. In March 2011, Daliresp® gained FDA approval in the USA, but had no effect on health-related
quality of life or systemic for reducing COPD exacerbations. Similar effects were seen in patients who received roflumilast in addition to salmeterol or tiotropium. Although effective in clinical trials, roflumilast produced several dose-limiting side effects and development is continuing in an attempt to minimize the incidence of side effects while retaining clinical efficacy.57

6.1.4 Chronic use of macrolide antibiotics

Acute COPD exacerbations are also treated with antibiotics. Among these medicines, macrolide antibacterials exert anti-inflammatory or immunomodulatory effects. Clinical effects have also been observed in COPD patients.

6.1.5 Other Pharmacologic Treatments

Vaccines

Vaccinations against influenza and pneumococcus are recommended in NICE guidelines for COPD.58 Despite a level A recommendation by the Centers for Disease Control and Prevention, the use of pneumococcal polysaccharide vaccination in patients with COPD is supported by limited data.

To date no randomized-controlled trial of pneumococcal vaccination for COPD patients has demonstrated any beneficial effect. The implementation of a pneumococcal vaccine trial in the COPD population is problematic because of the large sample size required for studies examining clinical outcomes and the fact that no adequate in vitro assays have been available to serve as surrogate measures of vaccine protection.

However, new laboratory methods have been developed and more accurate determination of the immunogenicity of pneumococcal vaccines is now possible. There is considerable interest in the development of an improved pneumococcal vaccine for patients with COPD, and advances in vaccine design hold considerable promise for improved prevention against pneumonia and acute exacerbations caused by Streptococcus pneumonia.

A recent study analysis of the Health Improvement Network (THIN) database was used to test if influenza and/or pneumococcal vaccination was associated with a reduced risk of all-cause mortality in COPD. The former, but not the latter was associated with reduced risk.59

For all-cause mortality the adjusted relative risks associated with influenza vaccination were 0.59 (95% CI 0.57 to 0.61) during the influenza season and 0.97 (95% CI 0.94 to 1.00) outside the season in patients not vaccinated against pneumonia, and 0.30 (95% CI 0.28 to 0.32) and 0.98 (95% CI 0.96 to 1.11), respectively, in patients vaccinated against pneumonia. The relative risk associated with pneumococcal vaccination was greater than one at all times of the year.

These results are unlike a recent Cochrane review 60 which showed no effect of influenza vaccination on mortality. NICE guidelines advise vaccination of patients with chronic obstructive pulmonary disease against influenza and Pneumococcus.
Mucolytic (mucokinetic, mucoregulator) agents (ambroxol, erdosteine, carbocysteine, iodinated glycerol).

Most studies showed no effect of mucolytics on lung function or symptoms, although some old studies have reported a reduction in the frequency of acute exacerbations.\textsuperscript{61, 62, 63}

Mucolytics do not have any significant adverse effects. The evidence suggests that if patients take these medicines regularly through the winter months this could result in a 21% reduction in the number of exacerbations, especially in people not already taking inhaled corticosteroids. These medicines do not alter the loss of lung function in COPD, but they are very safe and well tolerated.\textsuperscript{64}

### 6.1.6 Summary of Cochrane Reviews

Various Cochrane Reviews on the subject of COPD are summarized in Annex 6.13.2. Annex 6.13.2 lists presents the risk ratios (relative risk and odds ratios) and their respective 95% confidence intervals for 11 Cochrane Reviews, consisting of 30 different summaries of placebo-controlled clinical trials testing various treatments. The data in Annex 6.13.2 are visualized as Figure 6.13.3, below in which the risk ratios are Relative risks (trials #1-13) and Odds ratio for trials #14-30 (trial #1 on the left side of the X axis):

Beta-2-agonists for acute bronchitis (#1-3), tetracyclines as prophylactic therapy (#4), any antibiotic as prophylactic therapy (#5) any antibiotic for acute bronchitis (#6-10), fluticasone/salmeterol for COPD (#11-12), budesonide/formoterol for COPD (#13-14), mucolytics for COPD (#15-16), systemic corticosteroids for COPD (#17-18), tiotropium for chronic COPD (#19-21), inhaled corticosteroids for COPD (#22), tiotropium for stable COPD (#23-25), oral corticosteroids (#26-27), salmeterol for COPD (#28-29), phosphodiesterase 4 inhibitors-roflumilast or cilomilast for COPD (#30). Ratios greater than one are beneficial events (See Background Chapter 4).
KEY POINTS:

- To date, only two interventions—smoking cessation and long term treatment with oxygen (in people with hypoxaemia)—have been found to alter the long term course of chronic obstructive pulmonary disease and neither of these are considered. We do not consider pulmonary rehabilitation in this review, which is a standard-of-care in COPD patients and involves components such as patient assessment, exercise training, education, nutritional intervention, and psychosocial support.\(^{45}\)

- RCTs found short term benefits (as opposed to long term effects on progression) from: anticholinergic drugs, beta-2 agonists, inhaled corticosteroids (alone and in combinations with LABAs); oral steroids and an oral PDE4 inhibitor. The effects of anticholinergic drugs and beta-2 agonists are not seen in all people with chronic obstructive pulmonary disease, and the two agents combined are slightly more effective than either alone.

- Adverse effects and the need for frequent monitoring of blood concentrations limit the usefulness of theophyllines. There are similar adverse events challenges for the recently launched oral PDE4.

- It is not clear that anticholinergic agents affect decline in lung function; mucolytics have been shown to reduce the frequency of exacerbations, but with a possible deleterious effect on lung function; beta-2 agonists, oral corticosteroids, and antibiotics have not yet been evaluated for their long term effects.
7. What is the Current “Pipeline” of Products that Are to Be Used for this Particular Condition?

7.1 Pre-clinical and Clinical Development of novel targets

Substantial unmet needs remain in COPD. Although new products might confer significant advantages over the currently available treatments, there is still a huge unmet need for medicines that prevent the progression of COPD. Drug development for COPD is difficult owing to the chronic and slowly progressive nature of the disease; therefore, large studies carried out over long periods are needed to obtain the necessary statistical power to identify improvements.

- However, the targets listed below all suffer from the lack of drug development tools to identify patients likely to benefit from therapy as well as to predict long term efficacy.

Recent advances in understanding the pathogenetic mechanisms that underlie COPD have led to the identification of many novel therapeutic targets and exploration of alternative treatment pathways in recent clinical trials world-wide and have several novel classes of medicines for COPD in development including inhibitors of oxidative stress, leukotriene B4 receptors, and chemokine receptors, which are involved in the migration of inflammatory neutrophils in COPD, and inhibitors of phosphodiesterase 4 (PDE4), and p38 MAP Kinase, a significant anti-inflammatory target.66

Enhanced disease modification is expected from other inflammatory blockers that includes agents targeting CD8+ T cells, and inhibitors of NF-κB, chemokine-receptors, and T-helper-17 cells. Peroxisome proliferator-activated receptors (i.e. PPARγ, PPARα, and PPARδ) belonging to the nuclear receptor superfamily, and there is now sufficient evidence that the activation of these receptors induces antiinflammatory and immunomodulatory effects in the lung as well as in other tissues.67

Indeed, classes of drugs that are used for cardiovascular disease may be useful in COPD. Observational studies suggest that COPD patients treated with statins, angiotensin-converting enzyme inhibitors, and angiotensin II type 1 receptor blockers, and β-adrenoceptor blockers may have improved survival and reduced hospitalization from exacerbations. 68

- From a diagnostic point of view, specific disease biomarkers, improved methods for early detection and diagnosis of exacerbations, and enhanced understanding of the relations between COPD and comorbidities are considered by academics, regulators, and industry experts as critical. 69

- Additionally, an important question that so far remains unanswered is whether different phenotypes of the disease exist and, if so, whether they respond differently to treatment. There is clear evidence supporting the heterogeneity of the disease (e.g. frequent/infrequent exacerbates, persistent systemic inflammation, 70 and the requirement for a more personalized medicine approach.71
Table 6.13.1: Drugs in Development for COPD in 2010

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Clinical development</th>
</tr>
</thead>
<tbody>
<tr>
<td>LTB$_4$ antagonists</td>
<td>development stopped</td>
</tr>
<tr>
<td>Anti-TNF</td>
<td>development stopped</td>
</tr>
<tr>
<td>CXCR2 antagonists</td>
<td>in early clinical development</td>
</tr>
<tr>
<td>MMP-9 inhibitors</td>
<td>in early clinical development</td>
</tr>
<tr>
<td>Neutrophil elastase inhibitor</td>
<td>in early clinical development</td>
</tr>
<tr>
<td>PDE4 inhibitors</td>
<td>phase III trials but side effects</td>
</tr>
<tr>
<td>p38 MAPK inhibitors</td>
<td>phase I studies but problems with side effects and toxicity</td>
</tr>
<tr>
<td>NF-κB (IKK2) inhibitors</td>
<td>pre-clinical but concerns about side effects</td>
</tr>
<tr>
<td>PI3K-γ/δ inhibitors</td>
<td>early clinical development</td>
</tr>
<tr>
<td>PPAR-γ agonists</td>
<td>already developed for diabetes, clinical studies in progress</td>
</tr>
</tbody>
</table>


A list of medicines for COPD was located in the United States clinical trials database\(^72\) December 2102: open enrollment trials with patients still being recruited, all phases, interventional drug trials only: See Annex 6.13.3, also in Table 6.13.2. Table 6.13.2 is different than Table 6.13.1, most likely because the former relates to trials that have already provided results and the latter relates to trials that are still in the process of enrollment.

* “Phase 4” trials are post approval studies.

Table 6.13.2: List of medicines in United States clinical trials still open for enrollment.

<table>
<thead>
<tr>
<th>Phase 1</th>
<th>simvastatin (HMG-CoA reductase inhibitor-lowers cholesterol)</th>
<th>VA Loma Linda Health Care System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1</td>
<td>RV568 (Inhaled, narrow-spectrum kinase inhibitor)</td>
<td>Respivert Ltd</td>
</tr>
<tr>
<td>Phase 1</td>
<td>Tiotropium (high dose) + Olopatadine</td>
<td>Boehringer Ingelheim Pharmaceuticals</td>
</tr>
<tr>
<td>Phase 1</td>
<td>Cyclosporine (reversible inhibitor of interleukin-2 synthesis)</td>
<td>University of Pittsburgh</td>
</tr>
<tr>
<td>Phase 1</td>
<td>V0162 (anticholinergic compound)</td>
<td>Pierre Fabre Medicament</td>
</tr>
<tr>
<td>Phase 1</td>
<td>Quercetin (flavonoid antioxidant)</td>
<td>University of Michigan</td>
</tr>
</tbody>
</table>
## Phase 2

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Company Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEP03 (5-lipoxygenase inhibitor)</td>
<td>PharmaEngine</td>
</tr>
<tr>
<td>GW685698 Fluticasone Furoate/GW642444 Vilanterol</td>
<td>GlaxoSmithKline/GlaxoSmithKline</td>
</tr>
<tr>
<td>Tetomilast (phosphodiesterase-4 inhibitor)</td>
<td>Otsuka Pharmaceutical Development &amp; Commercialization, Inc.</td>
</tr>
<tr>
<td>Rosuvastatin (HMG-CoA reductase inhibitor-lowers cholesterol)</td>
<td>University Hospital, Akershus/AstraZeneca/Haukeland University Hospital, Bergen</td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
<td>Medical University of Vienna</td>
</tr>
<tr>
<td>BCT197</td>
<td>Novartis Pharmaceuticals</td>
</tr>
<tr>
<td>Iodinated Active Charcoal (IodoCarb)</td>
<td>PharmaLundensis AB</td>
</tr>
<tr>
<td>Roflumilast (phosphodiesterase-4 inhibitor)</td>
<td>Nycomed (Takeda)</td>
</tr>
<tr>
<td>Losmapimod (oral p38 MAP kinase inhibitor)</td>
<td>Cambridge University Hospitals NHS Foundation Trust/Technology Strategy Board/GlaxoSmithKline/Royal Brompton &amp; Harefield NHS Foundation Trust</td>
</tr>
<tr>
<td>PH-797804 (p38 MAP kinase inhibitor)</td>
<td>Pfizer</td>
</tr>
<tr>
<td>AZD5423 (inhaled selective glucocorticoid receptor agonist)</td>
<td>AstraZeneca</td>
</tr>
<tr>
<td>QMF149 (indacaterol maleate/mometasone furoate)</td>
<td>Novartis Pharmaceuticals</td>
</tr>
<tr>
<td>Glycopyrronium bromide (anticholinergic)</td>
<td>Prosonix Limited</td>
</tr>
<tr>
<td>TD-4208 (inhaled, long-acting muscarinic antagonist)</td>
<td>Theravance</td>
</tr>
<tr>
<td>CHF6001 (phosphodiesterase 4-inhibitor)</td>
<td>Chiesi Farmaceutici S.p.A.</td>
</tr>
</tbody>
</table>

## Phase 3

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Company Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erdosteine (mucolytic)</td>
<td>Edmond Pharma</td>
</tr>
<tr>
<td>Simvastatin (HMG-CoA reductase inhibitor-lowers cholesterol)</td>
<td>National Heart, Lung, and Blood Institute (NHLBI)</td>
</tr>
<tr>
<td>Fluticasone furoate/vilanterol (inhaled corticosteroid/long-acting β2 agonist)</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>Prednisolone (precursor to corticosteroid)</td>
<td>Hopital Universitaire Fattouma Bourguiba</td>
</tr>
<tr>
<td>Fluticasone/Formoterol (corticosteroid/long acting β2-agonist)</td>
<td>Ache Laboratorios Farmaceuticos S.A.</td>
</tr>
</tbody>
</table>
## Update on 2004 Background Paper, BP 6.13 COPD

<table>
<thead>
<tr>
<th>Phase 3</th>
<th>Moxifloxacin (synthetic fluoroquinolone antibacterial)</th>
<th>University College, London</th>
<th>University College, London</th>
<th>Royal Free Hampstead NHS Trust</th>
<th>University of Cambridge</th>
<th>National Institute for Health Research, United Kingdom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 3</td>
<td>Roflumilast (phosphodiesterase-4 inhibitor)</td>
<td>Nycomed: A Takeda Company</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 3</td>
<td>glycopyrronium bromide (anticholinergic)</td>
<td>Novartis Pharmaceuticals</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 3</td>
<td>Tiotropium/olodaterol (long-acting anticholinergic/long acting β2 agonist)</td>
<td>Boehringer Ingelheim Pharmaceuticals</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 3</td>
<td>Tiotropium (long-acting anticholinergic)</td>
<td>Boehringer Ingelheim Pharmaceuticals</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 3</td>
<td>theophylline (phosphodiesterase inhibitor)</td>
<td>Hospital Son Espases</td>
<td>Spanish Research Center for Respiratory Diseases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 3</td>
<td>aclidinium bromide (muscarinic antagonist)</td>
<td>Daewoong Pharmaceutical Co. LTD.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 3</td>
<td>GSK573719 (umeclidinium: long-acting muscarinic antagonist)</td>
<td>GlaxoSmithKline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 3</td>
<td>Zabofloxacin (fluoroquinolone antibiotic)</td>
<td>Dong Wha Pharmaceutical Co. Ltd.</td>
<td>Gachon University Gil Medical Center</td>
<td>The Catholic University of Korea Seoul St.Mary’s Hospital</td>
<td>Konyang University Hospital</td>
<td>Gangneung Asan Center</td>
</tr>
<tr>
<td>Phase 3</td>
<td>Fluticasone Furoate (inhaled corticosteroid)</td>
<td>GlaxoSmithKline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 3</td>
<td>Indacaterol Maleate/Glycopyrronium Bromide (long acting β2 agonist/anticholinergic)</td>
<td>Novartis Pharmaceuticals</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 3</td>
<td>GSK573719 (umeclidinium + vilanterol) (long-acting muscarinic antagonist/long-acting beta-2 agonist)</td>
<td>GlaxoSmithKline</td>
<td></td>
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</tbody>
</table>

Source: United States clinical trials database

### 7.2 Current and future market analysis

Inhaled corticosteroid/long-acting 2-agonist (ICS/LABA) combinations constitute the leading class in terms of sales, and are set to remain the dominant class until at least 2016, generating approximately one-third of total market sales over this period. The leading ICS/LABA combination product is GlaxoSmithKline’s Advair/Seretide® (fluticasone/salmeterol) with US$ 6.3 billion sales in 2006, making it the top-selling respiratory drug that year and the
third best-selling drug globally. In 2011, combined sales of these therapies constituted nearly two-thirds of the global COPD market.

The market for COPD will increase from nearly US$ 9 billion in 2011 to US$ 13.3 billion in 2021 in the United States, France, Germany, Italy, Spain, the United Kingdom, and Japan. Growth in the market will be in part driven by uptake of a new drug class—fixed-dose combination inhalers containing a long-acting beta-2 agonist (LABA) and a long-acting muscarinic antagonist (LAMA)—that will launch in 2014 and offer more potent bronchodilation than currently available treatments. In 2019, LABA/LAMA combinations are expected to become the sales-leading drug class in COPD.

Several new long-acting beta-2 agonist (LABA)/inhaled corticosteroid (ICS) combinations will probably be launched in the major markets, including such as GlaxoSmithKline/Theravance’s vilanterol/fluticasone furoate and Novartis’s indacaterol/mometasone. Several new monotherapies from existing classes will reach the COPD market also, such as long-acting muscarinic antagonists (LAMAs) including once-daily Novartis/Eisai’s glycopyrronium (Seebri®; See Table 6.13.2) and GlaxoSmithKline’s umeclidinium.

Governments and private insurance payers are increasingly reluctant to pay for higher-priced therapies without strong evidence that the drug is more efficacious or safer than competitors. This is easier to demonstrate for specific subpopulations, which in turn drives increased market segmentation, dividing it into a number of niches with high unmet needs. In turn, drug developers targeting current unmet needs must focus on developing targeted therapies to treat subpopulations. Key examples of unmet needs include:

- Efficacious anti-inflammatories for COPD (given that current therapies neither arrest nor reverse inflammation and the resulting decline in lung function or health status)
- Finding better ways to prevent and control COPD exacerbations
- Developing therapies for the 10% of patients with refractory asthma whose symptoms cannot be controlled with currently available medicines

Although higher-priced niche therapies will power future market growth, in-house R&D productivity and innovation capture remain key issues for big pharmaceutical companies developing respiratory medicines.

- Part of this problem has been the lack of novel validated targets and drug development tools after significant delays and failures in developing classes such as phosphodiesterase 4 (PDE4) inhibitors.
- Big pharmaceuticals has, therefore, chosen to be more conservative approach and invest in management of currently marketed medicines, and developing next-generation versions of well-established classes such as ICS/LABAs (for example, GlaxoSmithKline’s ‘Beyond Advair’ fluticasone furoate/vilanterol programme).
- As a result of big pharmaceutical’s bias towards low risk efforts in COPD, genuinely novel pipeline medicines for COPD are scarce among such companies. It could be argued that, instead, future innovation is likely to be primarily captured by smaller companies.
- However, the problem remains that smaller biotechnology and ‘small molecule’ companies simply cannot afford large scale studies. There is a risk that in the absence of new approaches, nobody would develop medicines for COPD.
8. What is the Current Status of Institutions and Human Resources Available to Address the Disease?

8.1 Institutions

8.1.1 Global Initiative on Obstructive Lung Disease (GOLD)\textsuperscript{75}

GOLD, a collaboration between the National Heart, Lung and Blood Institute, National Institutes of Health, USA, and the World Health Organization, has a mission to create a set of evidence-based guidelines. The GOLD committee is composed of leading experts from many nations around the world. The GOLD Guidelines recommend effective COPD management and prevention strategies. It strives to increase awareness of the medical community, public health officials, and the general public that COPD is a public health problem. The objective is to reduce morbidity and mortality from COPD through implementation and evaluation of effective programs for diagnosis and management. GOLD has recently released a new strategy for the management of COPD which reflects improved disease understanding and a more holistic approach relative to 2006 guidelines.\textsuperscript{75}

8.1.2 Canadian Thoracic Society COPD Guidelines\textsuperscript{76}

The Canadian Guidelines were designed to meet the specific need of Canadians in the context of their available resources. While recognizing GOLD as exemplary, their panel felt the need to improve upon specific aspects of the GOLD document. They specifically sought to develop a new chronic care model to replace the existing reactive acute care models.

8.1.3 American Thoracic Society - European Respiratory Society: Standards for Diagnosis and Management of Patients with COPD\textsuperscript{77}

See also Appendix 6.13.4.

This is a combined effort of both societies to create a web-based, live modular document that emphasizes some of the issues important to USA and European audiences. This guideline is sponsored by the American Thoracic Society and European Respiratory Society and was approved by the boards of both societies. It had input from clinicians, researchers, nurses and respiratory therapists. Some of these individuals also served on GOLD.

8.1.4 National Institute for Clinical Excellence (NICE), United Kingdom: Management of COPD in Adults in Primary and Secondary Care\textsuperscript{78}

National Institute for Health and Clinical Excellence (NICE) creates guidelines available as PDF files that are downloadable from their website.

8.2 Private Sector

Some of the largest pharmaceutical companies in the world (Pfizer, Novartis, AstraZeneca, Takeda, Boehringer Ingelheim, GlaxoSmithKline, Schering Plough) are involved on R&D directed to respiratory conditions, including COPD. They understand that, because of its chronic and progressive nature, COPD represents a massive and growing burden, both in direct and indirect costs. In developing countries where smoking continues to be extremely
prevalent, COPD is on the increase. It is difficult to ascertain exactly how much private sector R&D is relegated to COPD, as the available information (usually in the form of annual reports or SEC filings) usually do not separate out R&D expenses into specific disease conditions.

Several companies are investing financially and collaborating in pre-competitive efforts to improve disease understanding and develop drug development tools through international consortia including the COPD Foundation Biomarker Consortium, NHLBI’s SPIROMICS and COPDGene, CanCOLD, ECLIPSE, and IMI’s PROActive. In short, there is evidence of investment by GSK, as well as Pfizer, BI, Novartis, and Astra Zeneca in disease understanding studies. This investment of funding and human resources are well beyond most public funding.

8.3 Public Funding

8.3.1 Funding Sources: Europe

Framework Programmes:

Health research is financed (See also Chapter 2) by the current Seventh Framework Programme (FP 7) for Research and Technological Development 2007-2013 at about 50 billion euros. The future Horizon 2020, the Framework Programme for Research and Innovation (2014-2020) is set at about 80 billion euros.

Within the FP7 Health programme, two projects, EVA "Markers for emphysema versus airway disease in COPD"79 and COPACETIC "COPD Pathology: Addressing Critical gaps, Early Treatment and Innovative Concepts"80 have received cumulative funding of 12 million euros. At the same time, the FP7 Information and Communications Technology (ICT) programme funded a large-scale project AirPROM "Airway Disease Predicting Outcomes through Patient Specific Computational Modelling"81, in which 34 partners from the already existing consortia of the FP7 project EVA, IMI project U-BIOPRED,82 and the British Thoracic Society project Severe Asthma joined forces to build a model of airway disease for better diagnostics based on the genomics data and ex vivo models at the genome cell-tissue scale by applying tomographic (CT) and functional magnetic resonance imaging (MRI) coupled to detailed physiology at the tissue-organ scale utilizing Europe’s largest airway disease cohort. The project was awarded an 11.7 million euro grant.

Thus, total FP7 contribution to the study of COPD (2007-2012) was almost 59 million euros, of which the majority was provided to the collaborative projects (52.3 million), and 2.8 million was attributed to the frontier research grants by the European Research Council, while 3.8 million Euros has been distributed within the Marie Curie programme to support mobility, training, and knowledge transfer activities.

However, the actual extent of public funding for COPD-related R&D in Europe is difficult to estimate, although we have some limited information. In general, the amounts are far less than public funding in the United States. The second programme of ‘Community action in the field of health (2008-13)’ covering the period from 1 January 2008 to 31 December 2013 was established in October 2007. See Appendix 6.13.5.
Innovative Medicines Initiative

The PROactive project is a European project funded by the Innovative Medicines Initiative (IMI: See Chapter 2). Under this initiative, the PROactive consortium that includes academic government and industry members aims to improve care for COPD patients. PROactive will be developed with input from the regulatory authorities such as the European Medicines Agency (EMA). Once appropriately validated, PROactive will be used to evaluate the benefit of new treatments such as new medicinal products for COPD patients.83

The British Lung Foundation is the only charity in the UK that funds research into COPD-related topics.1 In 2011, out of total spending of about €8.5 million, scientific and medical research was funded with €2.2 million.

The UK Medical Research Council 84

The MRC receives annual ‘grant-in-aid’ funding from the UK Parliament. Although government-funded, the MRC is independent in its choice of which research to support. In 2011/2012, the MRC spent about €941 million on research. We summarize several MRC initiatives related to COPD:

1. The current inability to target therapy for COPD exacerbations means that some patients with COPD are inappropriately treated and this places a vulnerable population at risk. This is a one year study to assess mediators that can be measured in sputum and blood that are already known to closely relate to infections and inflammation (€728 289).

2. While corticosteroids are highly effective in suppressing airway inflammation in asthmatic patients, they are essentially ineffective in COPD. These studies should shed light on the molecular mechanisms of corticosteroid resistance in COPD, but may also be relevant to other chronic inflammatory diseases. They may also lead to new therapeutic approaches aimed at reversing this resistance mechanism (€350 035).

3. The London COPD Exacerbation Cohort (EXCEL Cohort) is a small established cohort of COPD patients recruited and specifically trained and monitored to report their attacks (exacerbations) to the research team to enable the exacerbation to be studied (and also the patient to receive treatment as quickly as possible) (€653 477).

The MRC is interested to promote focused priority setting in inflammatory disease research between academic researchers and the pharmaceutical industry. The workshops brought together a range of experts with an interest in COPD in order to identify challenges, barriers, and opportunities for collaboration. This resulted in the development of research consortia involving both academia and industry. The MRC has now invested €7.2 million in the COPD consortia over a four-year period.

1 Throughout Europe there are many organizations directed to providing educational and training materials related to COPD and therapeutic guidelines. Such organizations include the Alpha-1 Association (http://alpha1.org); Alpha-1 Foundation (more than $15million has been funded in Alpha-1 research http://www.alphaine.org); British Lung Foundation (http://www.lunguk.org); Global Initiative for Chronic Obstructive Lung Disease (GOLD) (define treatments; increase awareness and prevention of COPD worldwide http://www.goldcopd.com); EFA is the European Federation of Allergy and Airways Diseases Patients’ Associations, an alliance of 41 organizations in 23 different countries across Europe http://www.efanet.org).
The COPDMAP project was formed in 2011 as part of the UK Medical Research Council (MRC)/Association of the British Pharmaceutical Industry (ABPI) Inflammation and Immunology Initiative. Its purpose is to bring together academics and industry at the early R&D stages to develop a stratified approach to disease (targeting the right treatments to the right people), enabling effective clinical trials as well as identifying novel biomarkers, mechanisms and targets. ABPI Consortium members include Astra Zeneca, Pfizer, GlaxoSmithKline, Novartis, and Merck. Several areas of relevant research include: mechanisms, impact and therapeutic targeting of microbial and viral colonization in COPD, and elucidation of the mechanisms of defective innate immune responses and identification of novel therapeutic targets for COPD.

8.3.2: Funding Sources: United States

Research on COPD is funded through a number of federal programs, including the National Institutes of Health and its institutes such as primarily the National Heart Lung and Blood Institute (NHLBI).

The NHLBI Lung Diseases program supports research on the causes, diagnosis, treatment, and prevention of lung diseases and sleep disorders. Research areas include asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, critical care and acute lung injury, developmental biology and pediatric pulmonary diseases, immunology and fibrosis, lung cell and vascular biology, and pulmonary complications of AIDS and tuberculosis. In fiscal year (FY) 2011, the NHLBI funded research to explore common pathogenetic mechanisms of lung cancer and COPD.

The FY 2013 President’s Budget request for the NHLBI Lung Diseases program is $637.09 million, an increase of just $0.048 million or barely 0.01 per cent from the FY 2012 enacted level. See Appendix 6.13.6. To put this into context, the total NIH funding (all institutes including NHLBI) for COPD specifically is about $108 million for FY 2012 so this is about 16% of the “Lung Disease” program. In contrast, NIH funding (all institutes) for diabetes is about $1 billion for FY 2012.

Other sources of funding including industry support, private donors and organizations such as the COPD Foundation, Alpha-1 Foundation, Foundation of the American Thoracic Society, and the Chest Foundation.

COPD Biomarkers Quantification Consortium

The COPD Foundation embarked on the creation of a COPD Biomarkers Qualification Consortium (CBQC) in 2010. The CBQC is supported by member pharmaceutical companies (currently Astra Zeneca, Boehringer Ingleheim, GlaxoSmithKline, Novartis and Pfizer), each of which contribute financial support, unpublished clinical trial data and expertise. The consortium also includes experts from academia with the FDA, EMA, and NHLBI acting in an advisory role. The CBQC efforts were focused initially on three biomarker efforts: plasma fibrinogen for stratification of subjects at risk for hospitalization and mortality, six minute walk distance for stratification of subjects at risk for mortality, and St. George’s Respiratory Questionnaire (SGRQ) for subject stratification and as an outcome measure. The goal is to assemble data under the auspices of the Consortium that will permit official recognition of biomarkers that can improve disease monitoring and expedite new COPD.
The SPIROMICS Study\textsuperscript{67} SPIROMICS, which stands for Subpopulation and Intermediate Outcome Measures in COPD Study, was initiated by the National Heart, Lung and Blood Institute (NHLBI) along with several universities contracted as study sites. Among those participating in SPIROMICS are Columbia University, Johns Hopkins University, University of California Los Angeles, University of California San Francisco, University of Utah, Wake-Forest University, and University of Michigan. In addition, through a partnership established by the Foundation for the National Institutes of Health, several representatives of the pharmaceutical and biotherapeutic industry are participating as members of an external scientific board.

This study will recruit approximately 3,000 individuals of different backgrounds (men and women of different age groups and ethnicities) to assess their lung function, conduct CT scans and bronchoscopy, and take biochemical measurements from their blood, urine and sputum.

The COPDGene Study\textsuperscript{68}

COPDGene is a 21 site observational study designed to identify genetic factors associated with COPD. It will also characterize chest CT phenotypes in COPD subjects including assessment of emphysema, gas trapping, and airway wall thickening. Finally, subtypes of COPD based on these phenotypes will be used in a comprehensive genome-wide study to identify COPD susceptibility genes. COPDGene is intended to provide new information about genetic factors in COPD and will characterize the disease process using high resolution CT scans. Understanding genetic factors and CT phenotypes that define COPD will potentially permit earlier diagnosis of this disease and may lead to the development of treatments to modify progression.

9. Ways forward from a public health viewpoint with regard to Public Funding

9.1 Gaps between current research and potential research issues which could make a difference if eliminated.

- While new treatment initiatives have come from information on the physiology of COPD, \textit{not a single new therapy has come from information on pathogenic inflammatory processes.}

- Surrogate markers of inflammation, possibly derived from the analysis of sputum (cells, mediators, enzymes) or exhaled condensates (lipid mediators, reactive oxygen species, cytokines), that may predict the clinical usefulness of new management and prevention strategies for COPD need to be developed and qualification as tools in drug development will require a major investment in order to generate data in large cohorts and apply systems medicine to improve the application of emerging data.\textsuperscript{69}
Update on 2004 Background Paper, BP 6.13 COPD

- New clinical end points are needed to assess the impact of different COPD interventions. The cornerstone of clinical assessment has been a reduction in the decline of the forced expiration volume (FEV1) of the lung for inhaled corticosteroids and an improvement of FEV1 with bronchodilators. Both measures fail to take into account the multi-component nature of COPD. Rehabilitation therapy would have failed these tests despite its clear beneficial impact.

- Standardized methods for tracking trends in COPD prevalence, morbidity, and mortality over time need to be developed so that countries can plan for future increases in the need for health care services in view of predicted increases in COPD. This need is especially urgent in developing countries with limited health care resources.

- Since COPD is not fully reversible (with current therapies) and slowly progressive, it will become ever more important to identify early cases as more effective therapies emerge. Consensus on standard methods for detection and definition of early disease need to be developed.

- New medicines for the treatment of COPD are greatly needed and there has been an enormous effort now invested by the pharmaceutical industry to find such treatments. While preventing and quitting smoking is the obvious preferred approach, this has proved to be very difficult. Not all COPD is due to cigarette smoking, especially in low- and middle-income countries (LMIC).

- It is important to identify the genetic factors that determine why only a minority of heavy smokers develop COPD, and identification of genes that predispose to the development of COPD may provide novel therapeutic targets in the future.

- However, it will be difficult to demonstrate the efficacy of novel treatments on the rate of decline in lung function, since this requires large studies over many years. Hence, there is a need to develop novel outcome measures and surrogate biomarkers, such as analysis of sputum parameters (cells, mediators, enzymes) or exhaled condensates (lipid mediators, reactive oxygen species).

- Public health advocacy/research/evidence based on biomass/indoor air pollution is required as is this the major risk factor for COPD in women and younger persons.

9.2 What is the comparative advantage of the EU with regard to public funding of pharmaceutical R&D for COPD?

Given the scale of their human and economic costs, managing lung diseases should become a high priority for all European countries. The pharmaceutical industry is beginning to recognize this and it is probable that new and more effective therapies will become available, although not in the short term.

As the outlook is poor in the short and medium term for development of emerging therapies to treat or reverse COPD, the overriding imperative in low- and middle-income countries and in the expanded EU is to reduce the prevalence and incidence of smoking.
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2. BMJ Clinical Evidence, COPD http://clinicalevidence.bmj.com/x/systematic-review/1502/key-points.html


Update on 2004 Background Paper, BP 6.13 COPD


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### Annexes

#### Annex 6.13.1: Estimated population prevalence of GOLD stage II or higher COPD, separated by age

**Men**

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<td>3.30%</td>
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## Update on 2004 Background Paper, BP 6.13 COPD

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### Annex6.13.2: Cochrane Reviews on the subject of COPD

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<td>Becker LA, Hom J, Villasis-Keever M, van der Wouden JC. Beta-2-agonists for acute bronchitis. Cochrane Database offSystematic Reviews 2011, Issue 7. Art. No.: CD001726. DOI: 10.1002/14651858.CD001726.pub4</td>
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<td>placebo</td>
<td>Cough after seven days</td>
<td>RR</td>
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<td>Nine trials involving 1055 subjects</td>
<td>Tetracyclines</td>
<td>Placebo</td>
<td>Proportion of patients with exacerbations</td>
<td>RR: 1.11 (1.03 - 1.18)</td>
</tr>
<tr>
<td>Staykova T, Black PN, Chacko EE, Poole P.</td>
<td>Fifteen trials with 2618 patients</td>
<td>Any antibiotic prophylaxis</td>
<td>Placebo</td>
<td>Proportion of patients with exacerbations</td>
<td>RR: 1.09 (1.01 - 1.16)</td>
</tr>
<tr>
<td>Smith SM, Fahey T, Smucny J, Becker LA.</td>
<td>Nine studies</td>
<td>Any antibiotic</td>
<td>Placebo</td>
<td>Number of patients with cough</td>
<td>RR: 1.36 (1.15 - 1.51)</td>
</tr>
</tbody>
</table>

Prophylactic antibiotics in chronic bronchitis/COPD have a small but statistically significant effect in reducing the days of illness due to exacerbations of chronic bronchitis. They do not have a place in routine treatment because of concerns about the development of antibiotic resistance and the possibility of adverse effects. The available data are over 30 years old, so the pattern of antibiotic sensitivity may have changed and there is a wider range of antibiotics in use.

Antibiotics for acute bronchitis:

There was limited evidence to support the use of antibiotics in acute bronchitis. At follow-up, patients receiving antibiotics were marginally more likely to be clinically improved than those receiving placebo treatment.

Less likely to have cough with tx

Marginaly likely to be clinically improved

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcome</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith SM, Fahey T, Smucny J, Becker LA.</td>
<td>Fifteen trials with 2618 patients IN TOTAL</td>
<td>Any antibiotic prophylaxis</td>
<td>Placebo</td>
<td>Number of patients with night cough</td>
<td>RR: 1.33 (1.17 - 1.46)</td>
</tr>
<tr>
<td>Smith SM, Fahey T, Smucny J, Becker LA.</td>
<td>ANY antibiotic</td>
<td>Placebo</td>
<td>Number of patients with cough</td>
<td>Less likely to have cough with tx</td>
<td></td>
</tr>
<tr>
<td>Smith SM, Fahey T, Smucny J, Becker LA.</td>
<td>ANY antibiotic</td>
<td>Placebo</td>
<td>Number of patients clinically improved</td>
<td>Marginally likely to be clinically improved</td>
<td></td>
</tr>
</tbody>
</table>
 Antibiotics for acute bronchitis

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcome</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith SM, Fahey T, Smucny J, Becker LA.</td>
<td>ANY antibiotic vs placebo</td>
<td>Number of patients with abnormal lung exams</td>
<td>less likely to have abnormal lung exam</td>
<td>1.46 (1.3 - 1.59)</td>
</tr>
</tbody>
</table>

Antibiotics for acute bronchitis

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcome</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith SM, Fahey T, Smucny J, Becker LA.</td>
<td>ANY antibiotic vs placebo</td>
<td>Number of patients with limitations</td>
<td></td>
<td>1.25 (0.78 - 1.54)</td>
</tr>
</tbody>
</table>

Combined corticosteroid and long-acting beta-agonist

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcome</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nannini LJ, Cates CJ, Lasserson TJ, Poole P.</td>
<td>Fluticasone/salmeterol vs placebo</td>
<td>Rate of exacerbations</td>
<td>Compared with placebo, combination therapy led to a significant reduction of a quarter in exacerbation rates. There was a significant reduction in all-cause mortality with the addition of data from the TORCH trial.</td>
<td>0.74 (0.69 - 0.8)</td>
</tr>
</tbody>
</table>

Combined corticosteroid and long-acting beta-agonist

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcome</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nannini LJ, Cates CJ, Lasserson TJ, Poole P.</td>
<td>Budesonide/formoterol vs placebo</td>
<td>Rate of exacerbations</td>
<td></td>
<td>1.26 (1.12 - 1.38)</td>
</tr>
</tbody>
</table>

Combined corticosteroid and long-acting beta-agonist

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcome</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nannini LJ, Cates CJ, Lasserson TJ, Poole P.</td>
<td>Fluticasone/salmeterol vs placebo</td>
<td>Mortality</td>
<td></td>
<td>1.21 (1.02 - 1.35)</td>
</tr>
</tbody>
</table>
### Update on 2004 Background Paper, BP 6.13 COPD

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Authors</th>
<th>Details</th>
<th>Participants Randomised</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcome</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined corticosteroid and long-acting beta-agonist</td>
<td>Nannini LJ, Cates CJ, Lasserson TJ, Poole P.</td>
<td>Combined corticosteroid and long-acting beta-agonist in one inhaler versus placebo for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD003794. DOI: 10.1002/14651858.CD003794.pub3.</td>
<td>6427 participants randomised</td>
<td>Budesonide/formoterol placebo</td>
<td>Mortality</td>
<td>OR 1.22 (0.27 - 1.65)</td>
<td></td>
</tr>
<tr>
<td>Mucolytic agents chronic bronchitis or chronic obstructive pulmonary disease</td>
<td>Poole P, Black PN, Cates CJ.</td>
<td>Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2012, Issue 8. Art. No.: CD001287. DOI: 10.1002/14651858.CD001287.pub4.</td>
<td>30 trials in the review, recruiting a total of 7436</td>
<td>Mucolytic placebo</td>
<td>No exacerbations in study period (2-36 months) ALL studies</td>
<td>OR 1.88 (1.68 - 2.11)</td>
<td></td>
</tr>
<tr>
<td>Mucolytic agents chronic bronchitis or chronic obstructive pulmonary disease</td>
<td>Poole P, Black PN, Cates CJ.</td>
<td>Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2012, Issue 8. Art. No.: CD001287. DOI: 10.1002/14651858.CD001287.pub4.</td>
<td></td>
<td>Mucolytic placebo</td>
<td>No exacerbations in study period (2-36 months) STUDIES POST 2000</td>
<td>OR 1.24 (1.01 - 1.54)</td>
<td></td>
</tr>
<tr>
<td>Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease.</td>
<td>Walters JAE, Gibson PG, Wood-Baker R, Hannay M, Walters EH.</td>
<td>Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2009, Issue 1. Art. No.: CD001288. DOI: 10.1002/14651858.CD001288.pub3.</td>
<td>10 studies contributed data for analyses (n=1051) in TOTAL</td>
<td>Systemic corticosteroids placebo</td>
<td>Relapse within thirty days of original admission for COPD outpatients</td>
<td>OR 1.22 (0.69 - 1.54)</td>
<td></td>
</tr>
<tr>
<td>Systemic corticosteroids for acute exacerbations of chronic</td>
<td>Walters JAE, Gibson PG, Wood-Baker R, Hannay M, Walters EH.</td>
<td>Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews</td>
<td>Systemic corticosteroids placebo</td>
<td>Rate of relapse of exacerbation within 30 days</td>
<td></td>
<td>OR 1.22 (1.03 - 1.37)</td>
<td></td>
</tr>
</tbody>
</table>
**Update on 2004 Background Paper, BP 6.13 COPD**

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Clinical Outcome</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tiotropium versus placebo for chronic obstructive pulmonary disease.</strong></td>
<td>Number of patients with a clinically significant improvement (≥ 4 units) in quality of life (SGRQ)</td>
<td>1.54 (1.4 - 1.7)</td>
</tr>
<tr>
<td></td>
<td>Number of exacerbations Follow-up: 3 to 48 months</td>
<td>1.22 (1.13 - 1.3)</td>
</tr>
<tr>
<td></td>
<td>Number of patients with one or more exacerbations requiring hospitalisation Follow-up: 3 to 48 months</td>
<td>1.15 (1 - 1.28)</td>
</tr>
</tbody>
</table>

**Inhaled corticosteroids for stable chronic obstructive pulmonary disease.**

- *Yang IA, Clarke MS, Sim EH, Fong KM.*
  - Fifty-five primary studies with 16,154 participants
  - Inhaled corticosteroids placebo mortality OR
  - No consistent long-term benefit in the rate of decline in breathing capacity. Death rates were unchanged. Inhaled steroids were beneficial in slowing down the rate of decline in quality of life and reducing the frequency of exacerbations. Inhaled steroids increased the risk of side effects including thrush (candida) infection in the mouth and

- **Tiotropium** versus **placebo**
- **9 RCTs** (6,584 patients)
- **Tiotropium** reduces exacerbations and related hospitalisations and improves quality of life and symptoms in people with moderately severe COPD, **OR 0.65 (0.5 - 0.85)**


- **Tiotropium** versus **placebo**
- **COPD exacerbation**
- **Tiotropium** reduces exacerbations and related hospitalisations and improves quality of life and symptoms in people with moderately severe COPD, **OR 1.26 (1.17 - 1.34)**


- **Tiotropium** versus **placebo**
- **All cause mortality**
- **Tiotropium** reduces exacerbations and related hospitalisations and improves quality of life and symptoms in people with moderately severe COPD, **OR 1.27 (0.61 - 1.65)**


- **Oral corticosteroids** versus **placebo**
- **Withdrawal due to exacerbations COPD**
- There is no evidence to support the long-term use of oral steroids at doses less than 10-15 mg prednisolone though some evidence that higher doses (30 mg prednisolone) improve lung function over a short period. Potentially harmful adverse effects e.g., diabetes, hypertension, osteoporosis would prevent recommending long-term use at these high doses in most patients. **OR 0.44 (0.17 - 1.18)**


- **Oral corticosteroids** versus **placebo**
- **Patient FEV1 response greater than 20% from baseline with high dose**
- **Patient FEV1 response greater than 20% from baseline with high dose** **OR 2.74 (1.84 - 4.01)**

hoarseness, and the rate of pneumonia.
### Update on 2004 Background Paper, BP 6.13 COPD

<table>
<thead>
<tr>
<th>Disease</th>
<th>Oral Steroid Treatment</th>
<th>Details</th>
</tr>
</thead>
</table>
| Long-acting beta-2-agonists | | **Exacerbations**
| | **OR** 1.28 (1.1 - 1.43) | **Withdrawals due to lack of efficacy**
| | **OR** 0.25 (0.12 - 0.54) | **Likelihood of COPD exacerbation**

**Phosphodiesterase 4 inhibitors**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Oral Steroid Treatment</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>These medicines improve lung function and reduce the likelihood of a flare-up of COPD, however they have little effect on symptoms or quality of life over and above existing treatments. This may be due to side effects, although these are not serious.</td>
</tr>
</tbody>
</table>
### Annex 6.13.3: List of medicines in United States clinical trials

<table>
<thead>
<tr>
<th>Compound</th>
<th>Funder</th>
<th>Clinical Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aclidinium bromide</td>
<td>Schering-Plough, Novartis, Astra Zeneca,</td>
<td>Phase 3</td>
</tr>
<tr>
<td></td>
<td>Mayo Clinic, Boehringer Ingelheim,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Novartis</td>
<td></td>
</tr>
<tr>
<td>Arformoterol, tiotropium</td>
<td>Novartis</td>
<td>Phase 3</td>
</tr>
<tr>
<td>AZD1236</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AZD4818</td>
<td>Takeda, U. Florida</td>
<td>Phase 2</td>
</tr>
<tr>
<td>AZD9164</td>
<td>Dep’t Veterans Affairs (USA)</td>
<td>?</td>
</tr>
<tr>
<td>AZD9668</td>
<td>GlaxoSmithKline, Novartis, Takeda</td>
<td>Phase 3, 4*</td>
</tr>
<tr>
<td>Budesonide/formoterol</td>
<td>Novartis</td>
<td></td>
</tr>
<tr>
<td>Fluticasone</td>
<td>Astellas Pharma Inc</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Fluticasone propionate/salmeter</td>
<td>Boehringer Ingelheim</td>
<td></td>
</tr>
<tr>
<td>Glycopyrronium bromide</td>
<td>Novartis</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Glycopyrronium bromide</td>
<td>Novartis</td>
<td></td>
</tr>
<tr>
<td>Indacaterol</td>
<td>Novartis, Astra Zeneca Pfizer, NHLBI,</td>
<td>Phase 2, 3, 4</td>
</tr>
<tr>
<td></td>
<td>Takeda, Scheering-Plough, Fondiazone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Salvatore Maugeri, Forest Laboratories,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weill Medical College, Sunovion</td>
<td></td>
</tr>
<tr>
<td>Azithromycin</td>
<td>Merck</td>
<td>Phase 2</td>
</tr>
<tr>
<td>MP-376</td>
<td>Novartis</td>
<td>Phase 3</td>
</tr>
<tr>
<td>NVA237</td>
<td>Novartis, Sunovion, Astra Zeneca</td>
<td>Phase 2, 4</td>
</tr>
<tr>
<td>Roflumilast</td>
<td>Takeda, Astra Zeneca, Novartis</td>
<td>Phase 2, 3, 4</td>
</tr>
<tr>
<td>Tiotropium</td>
<td>Astra Zeneca, GlaxoSmithKline, Forest</td>
<td>Phase 2</td>
</tr>
<tr>
<td></td>
<td>Laboratories, U. Sao Paolo, Boehringer</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ingelheim, Novartis</td>
<td></td>
</tr>
<tr>
<td>Zileuton</td>
<td>Novartis</td>
<td>Phase 3</td>
</tr>
</tbody>
</table>
Appendices


Appendix 6.13.2  COPD: The New Workplace Epidemic - Education For Health (COPD Uncovered: Updated September 2011.)


Appendix 6.13.6  FY 2013 Budget, DEPARTMENT OF HEALTH AND HUMAN SERVICES NATIONAL INSTITUTES OF HEALTH National Heart, Lung, and Blood Institute (NHLBI)