

# Chronic Obstructive Pulmonary Disease (COPD)

## What is chronic obstructive pulmonary disease?

Chronic obstructive pulmonary disease (COPD) is a progressive, irreversible restriction of breathing, associated with abnormal inflammation of the lung in response to noxious particles or gases. Patients with COPD may have chronic bronchitis, emphysema and/or chronic asthma. There is therefore variability in its symptoms, but these typically include chronic cough, chronic sputum production and breathlessness.



Acute exacerbations, about half of them caused by bacterial infection, are common. Smoking is by far the most significant risk factor, followed by exposure to occupational dusts and chemicals and air pollution. A rare hereditary deficiency in alpha-1-antitrypsin may lead to the development of emphysema; other genetic factors have not been found in COPD.

## Who does COPD affect?

Accurate estimates of the prevalence of this disease are needed badly to anticipate the future burden of COPD, target key risk factors, and plan for providing COPD-related health services. In August 2007, the "Burden of Obstructive Lung Disease" or BOLD Initiative aimed to measure the prevalence of COPD and its risk factors and investigate variation across countries by age, sex, and smoking status. Nearly 10,000

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**Chronic Obstructive Pulmonary Disease is most commonly caused by smoking. The patient finds it harder and harder to breathe. Pharmaceutical companies are developing new medicines to improve the symptoms. In the future, it is to be hoped that patients with this disease can lead a less restricted life.**

participants from 12 countries were included to undergo spirometry testing and were also asked to fill a questionnaire about respiratory symptoms, health status, and exposure to COPD risk factors.

The prevalence of stage II or higher COPD in patients 40 years and older was found to be 10.1 per cent overall, 11.8 per cent for men, and 8.5 per cent for women. The worldwide study showed higher levels and more advanced staging of spirometrically confirmed COPD than have typically been reported. The epidemiologists reported that age and smoking are strong contributors to COPD, but they do not fully explain variations in disease prevalence. Although smoking cessation is becoming an increasingly urgent objective for an ageing worldwide population, a better understanding of other factors that contribute to COPD will therefore be crucial.

#### **Present treatments:**

No medication has been shown to halt or reverse disease progression in COPD, and the resulting lung damage is permanent. Treatment is mainly aimed at controlling symptoms and preventing acute exacerbations. Treatment guidelines generally classify COPD into mild, moderate and severe disease, according to the degree of airflow restriction and intensity of symptoms. The basis of therapy is a step-wise approach.

Short-acting inhaled bronchodilators (beta<sub>2</sub>-adrenoreceptor agonists or anticholinergics) are used to relax the airways on an 'as needed' basis in mild COPD. In moderate disease, regular bronchodilator use is supplemented by inhaled corticosteroid therapy. Antibiotics are prescribed during acute exacerbations if there are signs of infection. In addition, smoking cessation is vital in all cases, and is the only intervention that may slow disease progression.

The medications used to treat COPD are primarily those used to treat asthma, although not all asthma medicines are also approved for use in COPD. Leukotriene receptor antagonists, sodium cromoglycate and high-dose steroids are generally not used and long-acting beta<sub>2</sub> agonists and xanthines are less commonly employed than in asthma. Instead, short-acting, selective beta<sub>2</sub> agonists or anticholinergics are the usual starting point of therapy.

Market authorisations have been granted for combinations of selective beta<sub>2</sub> agonists plus corticosteroids, which were already established in asthma, and are inhaled by the patient. Such combinations have been shown to reduce overall death rates significantly and to reduce the number of acute exacerbations. Similarly, companies have developed other formulations such as dry powder or non-CFC inhaler forms that may offer advantages in terms of ease of use or reproducibility of dosing, like a new antimuscarinic M<sub>3</sub> receptor antagonist, a once-daily bronchodilator which has recently been marketed.

Long-term administration of oxygen may be needed in more advanced stages of COPD and can be effective in preventing the progression of complications such as raised blood pressure in the lungs, as well as in relieving symptoms of breathlessness. Vaccination against influenza and streptococcal pneumonia is also recommended, especially in the elderly, and has been shown to reduce death rates.

#### **What's in the development pipeline?**

Development of new long-acting and selective beta<sub>2</sub> agonists and anticholinergics continues. Several new beta<sub>2</sub> agonists and anticholinergics for potential once-a-day dosing are in development. Interestingly, researchers also study a compound in Phase 1 that combines the activities of a beta<sub>2</sub> agonist and an anticholinergic in a single molecule.

Another approach is a molecule with properties of a beta<sub>2</sub> agonist and nitric oxide releasing effects. Nitric oxide relaxes smooth muscle and the new compound has

been shown to protect against narrowing of the airways. Several new steroids are in Phase 2 development.

In addition, phosphodiesterase-4 (PDE-4) inhibitors are in several phases of clinical development as bronchodilators. The enzyme PDE-4 controls the activity of neutrophils, monocytes and macrophages, as well as smooth muscle cells and cells lining the airways, all of which are involved in the damaging over-reaction to smoke and dust seen in COPD. Unlike steroids and beta<sub>2</sub> agonists, PDE-4 inhibitors are often given by mouth.

Other new treatments are based on inhibiting the mediators of the inflammatory response in COPD. Interfering with such processes, or with the recruitment or function of the inflammatory cells, offers new approaches to treating COPD. Leukotriene B<sub>4</sub>, interleukin 8, tumour necrosis factor alpha and other cytokines are released during the inflammatory response and can damage lung structures irreversibly. Interfering with the recruitment or function of the inflammatory cells may thus provide a new means of treating COPD.

Studies with a 5-lipoxygenase inhibitor are ongoing, also with an adenosine A<sub>2</sub> agonist and a neurokinin-3 receptor inhibitor. Another class of action is the treatment with a leukotriene B<sub>4</sub> inhibitor, as well as a neurokinin NK<sub>1</sub>/NK<sub>2</sub> antagonist.

Finally, a variety of new medicines are being developed with the aim of improving the success rate of smoking cessation.

### **The longer-term future**

With the ageing of the global population the burden of COPD will increase in years to come. Prevalence estimates of the disorder show considerable variability across countries, suggesting that risk factors can affect populations differently. Other advances in the understanding of COPD are recognition of the importance of concomitant disease and understanding how factors other than lung function affect outcome in patients.

The field of COPD has seen a considerable burst of development activity in recent years and, taken together with the founding of the GOLD (Global Initiative for Chronic Obstructive Lung Disease) Initiative that has achieved consensus on many aspects of disease diagnosis, classification and treatment, there is reason to be optimistic about the chances to improve quality of life for the many people affected.

The development of a therapy that actually changes the progression of the condition will probably require a more thorough understanding of the very complex mechanisms involved in inflammation. Equally critical are improvements in diagnostic screening that are needed to identify the large number of people who are believed to be affected by COPD but are so far undiagnosed.



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