

Pharmacological treatment of chronic obstructive pulmonary disease

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Abstract: None of the drugs currently available for chronic obstructive pulmonary disease (COPD) are able to reduce the progressive decline in lung function which is the hallmark of this disease. Smoking cessation is the only intervention that has proved effective. The current pharmacological treatment of COPD is symptomatic and is mainly based on bronchodilators, such as selective β_2 -adrenergic agonists (short- and long-acting), anticholinergics, theophylline, or a combination of these drugs. Glucocorticoids are not generally recommended for patients with stable mild to moderate COPD due to their lack of efficacy, side effects, and high costs. However, glucocorticoids are recommended for severe COPD and frequent exacerbations of COPD. New pharmacological strategies for COPD need to be developed because the current treatment is inadequate.

Keywords: Chronic obstructive pulmonary disease, pharmacological treatment, bronchodilators, glucocorticoids, theophylline, antibiotics.

Introduction

The objective of pharmacological treatment of chronic obstructive pulmonary disease (COPD) is to prevent and control symptoms, reduce the frequency and severity of exacerbations, and improve general health status and exercise tolerance. None of the classes of drugs currently used in the treatment of COPD are able to modify the progressive decline in lung function which is the hallmark of this disease (Anthonisen et al 1994; Pauwels et al 1999; Vestbo et al 1999; Burge et al 2000). Smoking cessation is currently the only intervention which has been shown to reduce the progression of COPD (GICOPD 2001). To achieve this objective, behavioral therapy and pharmacological treatment such as the administration of bupropion (an antidepressant), and nicotine replacement therapy have proved useful (Jorenby et al 1999; Tashkin et al 2001). However, it is important to try to control symptoms of COPD with pharmacological treatment using the following general proposals (GICOPD 2001):

- 1) There should be a stepwise increase in treatment, according to the severity of the disease. The step-down approach used in the chronic treatment of asthma is not applicable to COPD.
- 2) Treatment needs to be chronic and maintained at the same level for long periods of time, unless significant side effects or exacerbations occur.
- 3) Since individual patient response to the pharmacological treatment is variable, it is important to monitor pharmacological treatment closely and, if necessary, adjust it frequently.

Drugs currently recommended for the treatment of COPD are:

- 1) Bronchodilators (selective β_2 -agonists, anticholinergic antimuscarinic agents and methylxanthines);
- 2) glucocorticoids;

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3) other types of medication (vaccines, antibiotics, α_1 -antitrypsin augmentation therapy, mucolytic agents, antioxidants, immunoregulators, antitussives and vasodilators).

These drugs will be presented in the order in which they would normally be prescribed for the treatment of patients with COPD, based on the level of severity of the disease. Current knowledge on inhibitors of phosphodiesterase type 4 (PDE4), a new class of drugs for COPD which are in the late phase III of clinical development (Lipworth 2005), will be presented. However, it must be emphasized that each treatment regimen needs to be patient-specific as the relationship between the severity of symptoms and the severity of lung function is influenced by other factors, such as the frequency and severity of exacerbations, the presence of complications, the presence of respiratory failure, the presence of other diseases, and general health status.

Treatment of stable chronic obstructive pulmonary disease

Bronchodilators

Bronchodilators are currently the mainstay of the treatment of COPD (GICOPD 2001). Bronchodilators are selective short-acting β_2 -agonists such as salbutamol, metaproterenol, terbutaline, bambuterol, pirbuterol, isoetharine, bitolterol and fenoterol or selective long-acting β_2 -agonists such as salmeterol and formoterol; anticholinergic antimuscarinic agents such as ipratropium bromide, oxitropium bromide and tiotropium bromide, and methylxanthines such as theophylline. Short- and long-acting β_2 -agonists and antimuscarinic agents are generally administered by inhalation (aerosol, dry-powder or nebuliser solution). Bronchodilator therapy is most frequently delivered by pressurized metered-dose inhalers (MDIs) or dry-powder inhalers (DPIs). Because of the lower bioavailability in asthma patients, the dose delivered by DPIs should be doubled compared with that of MDIs (RS 2003); while a study comparing ipratropium bromide delivered by MDIs and by DPIs in COPD patients found that there was no difference between these two types of inhalers (Cuvelier et al 2002). The use of a spacer device to improve drug delivery proves particularly useful for patients who have poor inhalation technique. In a study on patients with COPD, inhalation of salbutamol through MDIs with spacer and dry-powder inhalers produced similar bronchodilating effects (Ikeda et al 1999). However, further studies are necessary to establish deposition in the respiratory tract and the dose-

effect relationship of drugs delivered by different inhalers in patients with COPD, as these are important factors in the choice of dosage. Short-acting β_2 -agonists such as salbutamol and terbutaline are also available for oral or parenteral delivery. Theophylline is generally administered orally, mostly frequently in controlled release preparations which prolong the pharmacological effect of the drug, even if they do not significantly eliminate the interindividual variability of the bioavailability. For chronic administration, bronchodilators are the mainstay of treatment of COPD as they prevent and improve symptoms (Chrystyn et al 1988; Vathenen et al 1988; Gross et al 1989; Rennard 2004). One of the main therapeutic effects of bronchodilators, at least in severe COPD, is improvement in the emptying of the lungs during expiration. This causes a reduction in dynamic hyperinflation at rest and during exercise with consequent improvement in exercise tolerance (Belman et al 1996). However, it is not easy to predict the extent of this improvement based on an increase in forced expiratory volume in one second (FEV_1) after a short period of bronchodilatory therapy (Berger and Smith 1988; Hay et al 1992). The evaluation of the efficacy of bronchodilators is generally based on questionnaires concerning symptom variation. COPD may require inhalation of a short-acting β_2 -agonist on demand or, when airways obstruction is more severe, chronic administration of an antimuscarinic agent by inhalation or a long-acting β_2 -agonist (RS 2003).

Selective β_2 -agonists

There are no significant differences between the various β_2 -agonists as far as selectivity for β_2 -adrenoceptors is concerned, with the exception of metaproterenol and isoetharine, which are less selective (Undem and Lichtenstein 2001). Short-acting β_2 -agonists have a bronchodilatory effect within 1 to 5 minutes and which lasts for up to 4 hours (Rennard 2004). Long-acting inhaled β_2 -adrenergic agonists such as salmeterol and formoterol have a prolonged bronchodilatory effect for approximately 12 hours. Unlike salmeterol which has a slow onset of action, formoterol has a rapidly occurring bronchodilatory effect similar to that of short-acting β_2 -agonists (Undem and Lichtenstein 2001; Rennard 2004). Selective β_2 -agonists mainly work by stimulating the β_2 -adrenoceptors on the airway smooth muscle cells. The formation of the drug-receptor complex activates a stimulatory protein (Gs) which binds to guanosine triphosphate (GTP) with activation of the adenylate cyclase which leads to an increase in intracellular cyclic adenosine

monophosphate (cAMP) levels which, in turn, activates a cAMP-dependant protein kinase (PKA) (Johnson and Coleman 1995). Activation of the latter causes myosin light chain kinase phosphorylation with a reduction in the affinity of this enzyme for the calcium–calmodulin complex, a reduction in the formation of active myosin light chain kinase, a reduction in myosin phosphorylation and, finally, a reduction in the interaction of actin and myosin filaments with consequent bronchodilation. In addition, PKA stimulation causes a reduction in intracellular calcium ion levels because of increased extrusion of calcium from the cell, reduction in the entry of calcium into the cell, and increase in the uptake of calcium by the smooth endoplasmic reticulum, which is the site at which calcium ions are deposited within the cell.

The reduction in the concentration of intracellular calcium causes a reduction in the formation of the calcium–calmodulin complex which produces the previously described effects. In addition to this main bronchodilation mechanism of selective β_2 -agonists, other mechanisms may, in theory, contribute to reducing airway obstruction. Stimulation of β_2 -adrenoceptors also increases potassium channel conduction with hyperpolarization and relaxation of the airway smooth muscle (Kume et al 1994). This effect is, in part, independent from the increase in cAMP levels (Kume et al 1994). The activation of β_2 -receptors on inflammatory cells such as mast cells, basophils, eosinophils, neutrophils and lymphocytes cause an increase in cAMP levels and subsequent inhibition of the release of inflammatory mediators such as leukotrienes, histamine and cytokines (Hughes et al 1983; Barnes 1999). β_2 -agonists increase mucociliary clearance, decrease microvascular permeability and may inhibit phospholipase A_2 with subsequent reduction in the synthesis of leukotrienes, prostaglandins and thromboxane A_2 , which are important inflammatory mediators (Seale 1988). The importance of these mechanisms on the therapeutic effect of β_2 -agonists in humans, particularly in COPD, is not known.

Inhalation limits the absorption and therefore the systematic side effects of β_2 -agonists. However, only about 10% of the aerosol enters the respiratory tract while the remainder is swallowed and may be absorbed in the intestinal tract with consequent systemic side effects. Furthermore, aerosolized particles less than $1\mu\text{m}$ in diameter reach the alveoli and may be absorbed in the pulmonary capillaries. The main side effect of selective β_2 -agonists administered by inhalation at clinical doses is muscular tremor. However, this tends to diminish in intensity during prolonged

treatment. This phenomenon is known as drug tolerance. It is not known if drug tolerance is due to the down regulation of the β_2 -adrenoceptors on the muscle cytoskeleton or to adaptation phenomena in the central nervous system. Tachycardia is uncommon in clinical doses of β_2 -agonists administered by inhalation. The absorption of β_2 -agonists may cause tachycardia by stimulating the cardiac β_1 -adrenoceptors, particularly at higher doses when relative selectivity for β_2 -adrenoceptors is lost. Although there are fewer cardiac β_2 -adrenoceptors, their stimulation may also contribute to tachycardia (Undem and Lichtenstein 2001). This type of side effect is particularly relevant in patients with ischemic heart disease or pre-existing arrhythmias. In these patients, β_2 -agonists need to be administered with caution, even when inhaled. Bronchodilation may cause ventilation/perfusion mismatch with a consequent drop in the arterial partial pressure of oxygen. This is generally transitory and of little importance. Other side effects of systemically delivered β_2 -agonists, such as hypokalemia, increase in the plasma concentrations of glucose, lactose, and free fatty acids are much less common when β_2 -agonists are delivered by inhalation.

Antimuscarinic drugs

Antimuscarinics are delivered in the same way as bronchodilators. Antimuscarinics are quaternary ammonium derivatives which, after inhalation, undergo <1% absorption from the pulmonary or gastrointestinal tract. The parasympathetic nervous system has a role in the regulation of the bronchial tone. Vagal fibres activate nicotinic and M_1 muscarinic receptors on the parasympathetic ganglia of the respiratory tract; short postganglionic fibers release acetylcholine which stimulates the M_3 muscarinic receptors on the airway smooth muscle cells with consequent increase in motility. In addition, the airway submucosal glands have M_3 muscarinic receptors. M_3 muscarinic receptor stimulation increases bronchial secretion. Inflammatory mediators such as eicosanoids, histamine, and bradykinin may further produce parasympathetic reflexes which partly explains their bronchoconstriction effect. Antimuscarinic bronchodilators are non-selective antagonists of cholinergic muscarinic receptors. Their effect on airway obstruction is mainly due both to M_3 muscarinic receptor antagonism in the airway smooth muscle cells, with consequent bronchodilation, and to M_3 muscarinic receptor antagonism in the cells of the submucosal glands, with a reduction in the basal and stimulated cholinergic parasympathetic activity with

consequent reduction in airway obstruction. Unlike atropine, antimuscarinic bronchodilators do not have an inhibitory effect on mucociliary clearance. The reason for this difference is not known. The effectiveness of antimuscarinic drugs depends on the role that cholinergic vagal tone has in the pathophysiology of bronchial obstruction. Antimuscarinic bronchodilators are generally considered to be more effective for COPD than for asthma. This could be partly due to the different pathophysiological role of the parasympathetic vagal system in these two diseases. The aerosol inhalation of ipratropium has a maximum effect 30–60 minutes after administration; its duration of action is 3 to 6 hours, making administration of the drug necessary 3 to 4 times a day. Ipratropium generally produces the same moderate bronchodilation as obtained with maximum doses of β_2 -agonists (Undem and Lichtenstein 2001). Oxitropium produces similar pharmacological effects to ipratropium and can be administered twice a day. Tiotropium bromide, a new long-acting anticholinergic drug, which can be administered just once a day, has similar or greater efficacy compared with other bronchodilators (Calverley 2000) and is useful in combination with formoterol for COPD treatment (van Noord et al 2006). A randomized, prospective, double-blind, placebo-controlled, multicenter trial to assess whether adding salmeterol or salmeterol–fluticasone to chronic therapy with tiotropium would provide additional clinical benefit to patients with moderate to severe COPD is currently being carried out (Aaron et al 2004). Tiotropium improves sleeping arterial oxygen saturation (McNicholas et al 2004) and, in combination with pulmonary rehabilitation, exercise tolerance in patients with COPD (Casaburi et al 2005). Tiotropium bromide is indicated in the maintenance treatment of COPD, but it is not effective in relieving acute bronchospasms. However, as is the case with asthmatic patients, some authors raised doubts about chronic administration of bronchodilators which could be associated with worsening COPD (van Schayck et al 1991). Because of their negligible absorption, antimuscarinics rarely cause systemic side effects and are generally well tolerated. Possible side effects include dry mouth, nausea, constipation, and headache (RS 2003). Antimuscarinic bronchodilators should be administered with caution in glaucoma, benign prostatic hypertrophy and urinary obstruction (RS 2003; Rennard 2004). Cases of acute angle-closure glaucoma have been reported with nebulized ipratropium, particularly when given with nebulized salbutamol.

Theophylline

Theophylline, a methylxanthine, is one of the least expensive bronchodilators. Given its very low solubility in water, theophylline is administered intravenously as aminophylline. Aminophylline is a theophylline and ethylenediamine mixture, which is 20 times more soluble than theophylline alone. The bronchodilatory effect of theophylline is due both to relatively non-selective inhibition of cyclic nucleotide phosphodiesterases and to competitive antagonism of adenosine receptors (Barnes 2003). At least eleven phosphodiesterase isozymes have been identified (Soderling and Beavo 2000). The inhibition of phosphodiesterase isozymes type III and IV causes relaxation of the airway smooth muscle cells *in vitro* (Torphy et al 1993). Selective phosphodiesterase-4 inhibitors for COPD are currently in clinical trials (Lipworth 2005). Adenosine receptor antagonism also contributes to the bronchodilatory effect of theophylline (Feoktistov et al 1998). In addition to bronchodilation, theophylline may have anti-inflammatory effects at lower plasma concentrations in the respiratory tract as shown by the reduction both in the number of neutrophils and in the interleukin-8 concentration in induced sputum from COPD patients, where the same effects cannot be obtained after inhalation of high glucocorticoid doses (Barnes 2003). *In vitro* studies have shown that low doses of theophylline may enhance the anti-inflammatory effect of corticosteroids and antagonize the “resistance” to corticosteroids caused by smoking in COPD patients by activating histone deacetylases (Barnes 2003, 2006).

Theophylline is generally administered orally in conventional form or, more frequently, through sustained-release preparations or intravenously (like aminophylline) (Undem and Lichtenstein 2001). Sustained-release preparations are available for administration every 8, 12, or 24 hours. Intravenous administration of theophylline must be given very slowly, over at least a 20 minute period (RS 2003), because of the risk of serious toxic effects such as arrhythmias and convulsions. Inhalation of theophylline is not effective and intramuscular injection is not possible because of its irritant effect at the site of injection. Absorption of theophylline from conventional formulations is fast and complete with a plasma concentration peak within two hours of administration. Absorption of theophylline from sustained-release preparations has a large interindividual variability, for this reason, dosage must be changed to suit the individual patient. Theophylline is mainly

eliminated by hepatic metabolism (less than 15% is excreted in the urine unchanged) (Undem and Lichtenstein 2001). There is wide variation in the rate of elimination of theophylline. The half-life of elimination is on average 8 to 9 hours in adults and about 3.5 hours in children (Undem and Lichtenstein 2001). The half-life is increased in heart or liver failure, viral infections, in the elderly and with concomitant administration of some drugs such as cimetidine, ciprofloxacin, erythromycin, fluvoxamine, and oral contraceptives. The half-life of elimination of theophylline is decreased in smokers and in chronic alcoholics, and with concomitant administration of drugs such as phenytoin, carbamazepine, rifampicin, and barbiturates (RS 2003). In addition to bronchodilation, theophylline may increase cardiac contractility, have a psychostimulant or diuretic effect, and increase diaphragmic contractility. A possible therapeutic importance for COPD has been attributed to this last effect. However, theophylline has some disadvantages including its low therapeutic index which limits its administration. For this reason, and because of the large interindividual variability in its bioavailability, therapeutic monitoring of plasma theophylline concentrations is required. This involves taking regular blood samples after the theophylline concentrations reach a steady-state to ensure that the plasma theophylline concentration is within the therapeutic range for plasma theophylline concentrations for which the majority of patients obtain therapeutic effects without toxic effects, even though side effects are found with therapeutic concentrations. The therapeutic range for theophylline is between 10–20 µg/ml. Toxic side effects are associated with theophylline concentrations of more than 25 µg/ml. The risk of serious toxic effects, such as arrhythmias and convulsions, is high with theophylline concentrations of more than 40 µg/ml. At therapeutic plasma concentrations the main side effects of theophylline include anorexia, nausea, vomiting, insomnia, agitation, palpitation, and hypotension (Undem and Lichtenstein 2001).

Glucocorticoids

Inhaled glucocorticoids currently available include beclomethasone dipropionate, budesonide, flunisolide, fluticasone propionate and triamcinolone acetonide. There are no significant differences between these drugs in terms of their efficacy and tolerability (Undem and Lichtenstein 2001; RS 2003). Mometasone and ciclesonide, two new glucocorticoids in advanced clinical trials, seem to have a longer duration of action with the possibility of once a day

administration. Ciclesonide is a prodrug which is activated by a pulmonary esterase, with the possibility of increased selectivity of action and reduced systemic side effects resulting from glucocorticoid absorption. Glucocorticoids do not cause relaxation of the airway smooth muscle and therefore have no effect on acute bronchoconstriction. Glucocorticoids bind to specific cytoplasmic receptor proteins, which, in turn bind to regulatory proteins such as heat shock proteins and an immunophyllin (Undem and Lichtenstein 2001). The glucocorticoid–receptor interaction causes a receptor conformational change which leads to regulatory protein detachment, dimerization of the glucocorticoid receptor complexes and translocation to the nucleus where the drug–receptor complex binds to specific regulatory DNA sequences (glucocorticoid response elements, GRE), which modulate the expression of the adjacent genes. The time required for gene expression and protein synthesis explains the delayed effect of glucocorticoids which generally occurs several hours after administration. The anti-inflammatory mechanisms of action of glucocorticoids are largely due to the inhibition of gene expression which encodes for proinflammatory cytokines in the airway inflammatory cells (Undem and Lichtenstein 2001). Part of the anti-inflammatory effect of glucocorticoids may be due to the induction of lipocortin. Lipocortin is a protein which inhibits phospholipase A₂. Phospholipase A₂ enzymes cause cleavage of arachidonic acid from phospholipids in the plasma membrane. The arachidonic acid is the substrate for the synthesis of leukotrienes, prostaglandins, and thromboxane A₂, which are important inflammatory mediators. Although glucocorticoids are generally effective in asthma, the anti-inflammatory effect of glucocorticoids in COPD patients remains controversial and seems to be very limited (Pauwels et al 1999; Vestbo et al 1999; Burge et al 2000; LHSRG 2000). This seems to reflect a pathophysiological difference between COPD and asthma. It has been suggested, on the basis of *in vitro* studies, that oxidative stress and cigarette smoke, which both play an important role in the pathophysiology of COPD, induce resistance to the action of glucocorticoids through mechanisms which involve the acetylation of histones. Histones are nucleic proteins that are important regulators in gene expression (Barnes 2000, 2003). Furthermore, the variable effects of glucocorticoids on airway inflammation may be due to the heterogeneity of the disease and the limited reproducibility of markers of inflammation (Keatings et al 1997; Confalonieri et al 1998). What is certain is that glucocorticoids do not modify the

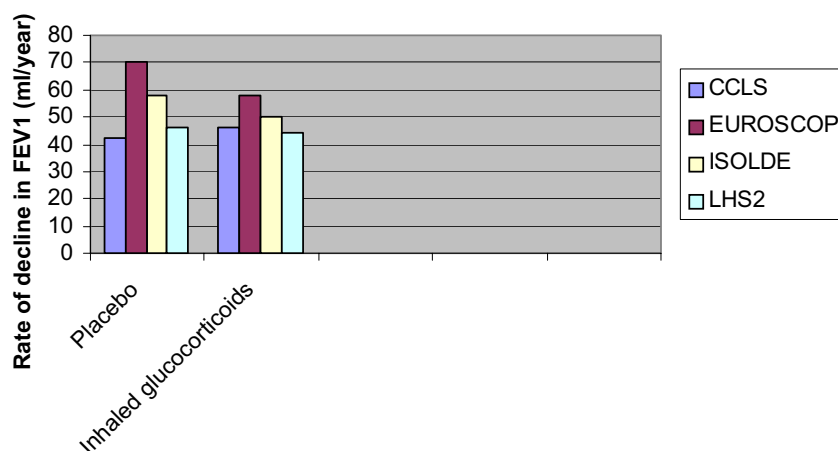


Figure 1 Rate of decline in forced expiratory volume in one second (FEV_1) after administration of placebo or inhaled glucocorticoids in four randomized controlled multicenter clinical trials: Copenhagen City Lung Study (CCLS), European Respiratory Society study On Chronic Obstructive Pulmonary disease (EUROSCOP), Inhaled Steroids in Obstructive Lung Disease (ISOLDE), and Lung Health Study 2 (LHS2). Inhaled glucocorticoids did not have a significant effect on the rate of decline in FEV_1 in any of the clinical trials.

natural history of COPD, as measured by the rate of decline in FEV_1 (Figure 1). Four large randomized placebo-controlled multicenter clinical trials (European Respiratory Society study on chronic obstructive pulmonary disease [EUROSCOP], Copenhagen City Lung Study, Inhaled Steroids in Obstructive Lung Disease in Europe [ISOLDE], and Lung Health Study 2 [Pauwels et al 1999; Vestbo et al 1999; Burge et al 2000; LHSRG 2000]) all found that inhaled glucocorticoids had no significant effects on the progressive decline in FEV_1 in patients with mild and moderate to severe COPD. One of these studies (Burge et al 2000) in patients with more severe COPD showed a reduction in the frequency of exacerbations (from 1.33 to 0.99 per year, a reduction of 25%). Other clinical trials with both fluticasone and budesonide showed that inhaled glucocorticoids reduce COPD exacerbation rate (Calverley, Pauwels, et al 2003; Jones et al 2003; Szafranski et al 2003), although the mechanism for this effect is currently unknown. However, an earlier study on a smaller sample showed a reduction in severity, but not in the frequency of exacerbations with inhaled glucocorticoids (Paggiaro et al 1998). From these clinical trials it is concluded that inhaled glucocorticoids should only be administered to patients with severe to very severe COPD (post-bronchodilator $FEV_1 \leq 50\%$ of the predicted value) with frequent exacerbations requiring treatment with antibiotics or oral glucocorticoids (GICOPD 2001). The dose of glucocorticoids required to reduce the frequency of exacerbations in these patients with COPD is not known (MacNee and Calverley 2003).

Improvement in airflow in patients with COPD after chronic treatment with inhaled glucocorticoids is very

modest (Pauwels et al 1999; Burge et al 2000). However, some studies reported further improvement in airflow when glucocorticoids are added to long-acting β_2 -agonist bronchodilators (Mahler et al 2002; Calverley, Pauwels, et al 2003; Szafranski et al 2003).

One study reported that withdrawal of fluticasone propionate from combined salmeterol-fluticasone treatment in patients with COPD resulted in acute and persistent deterioration in lung function and dyspnoea and in increase in mild exacerbations (Wouters et al 2005). However, median percentage predicted FEV_1 at start of the 3 month run-in period was about 50% implying that a considerable number of patients included in this study had moderate COPD ($FEV_1 \geq 50\%$ of the predicted value) for which inhaled glucocorticoids are not indicated (GICOPD 2001). On the other hand, all the patients in this study had a history of at least 2 COPD exacerbations in the last year treated with oral glucocorticoids and/or antibiotics which suggest chronic treatment with inhaled glucocorticoids (GICOPD 2001).

The effect of inhaled glucocorticoids on mortality for COPD is controversial and mainly based on retrospective data (Sin and Tu 2001; Soriano et al 2002; Fan et al 2003; Suissa 2003; Sin et al 2005). Prospective studies assessing the effect of inhaled glucocorticoids and long-acting β_2 -agonists, alone or in combination, on mortality in patients with COPD are in progress (Rennard 2004; Vestbo 2004).

Oral glucocorticoids are not generally recommended for the treatment of stable COPD due to their limited therapeutic effects and numerous systemic side effects.

Administration of inhaled glucocorticoids for patients with stable COPD must again be carefully considered because of possible side effects. Oropharyngeal candidiasis, due to the local immunosuppressive effect of glucocorticoids, is a common side effect. Oropharyngeal candidiasis is avoidable to a certain extent by using large volume spacers or rinsing the oropharynx with water after drug delivery. Even when delivered locally, such as by aerosolized inhaler, glucocorticoids may be partly absorbed with consequent systemic side effects due to their high lipid solubility. Particularly notable side effects include suppression of endogenous cortisol synthesis by inhibiting the hypothalamic–pituitary–adrenal axis, particularly at doses higher than 1500 µg/day (Undem and Lichtenstein 2001); the possibility of osteoporosis even at doses of 500 µg/day (Undem and Lichtenstein 2001); a slightly increased risk of glaucoma, particularly during long-term treatment at high doses, and of cataract (Undem and Lichtenstein 2001). Glucocorticoids, particularly at high doses, should be inhaled using a large-volume spacer which increases the profound deposition of the drug and reduces

drug deposition in the oropharynx, with a consequent reduction in the incidence of candidiasis. However, in the absence of proven efficacy and because of possible side effects, including systemic side effects, and high costs, there is no rational pharmacological basis for the use of inhaled glucocorticoids for all patients with stable COPD, and their use should be limited just to the cases previously described (GICOPD 2001).

Clinical considerations

The choice between β_2 -agonists, anticholinergic antimuscarinic agents, theophylline or drug combinations depends on individual patient response to the treatment. Pharmacological therapy at each stage of stable COPD according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines is shown in Figure 2 (Figure 2). Bronchodilator combinations may improve drug efficacy and reduce side effects, compared with an increase in the dosage of a single bronchodilator (COMBIVENT 1994).

For patients with COPD, long-acting β_2 -agonists delivered by inhalation, such as salmeterol and formoterol,

New	0: At Risk	I: Mild	II: Moderate	III: Severe	IV: Very Severe
Characteristics	<ul style="list-style-type: none"> • Chronic symptoms • Exposure to risk factors • Normal spirometry 	<ul style="list-style-type: none"> • $FEV_1/FVC < 70\%$ • $FEV_1 \geq 80\%$ • With or without symptoms 	<ul style="list-style-type: none"> • $FEV_1/FVC < 70\%$ • $50\% \leq FEV_1 < 80\%$ • With or without symptoms 	<ul style="list-style-type: none"> • $FEV_1/FVC < 70\%$ • $30\% \leq FEV_1 < 50\%$ • With or without symptoms 	<ul style="list-style-type: none"> • $FEV_1/FVC < 70\%$ • $FEV_1 < 30\%$ or $FEV_1 < 50\%$ predicted plus chronic respiratory failure
	Avoidance of risk factor(s); influenza vaccination				
		Add short-acting bronchodilator when needed			
			Add regular treatment with one or more long-acting bronchodilators Add rehabilitation		
				Add inhaled glucocorticosteroids if repeated exacerbations	
					Add long-term oxygen if chronic respiratory failure Consider surgical treatments

Figure 2 Pharmacological treatment of stable COPD based on GOLD guidelines. Adapted from GICOPD (2001).

significantly improve symptoms, exercise tolerance and general health status (Cazzola et al 1995; Ulrik 1995; Boyd et al 1997). Both β_2 -agonists and long-acting anticholinergics reduce the frequency of exacerbations in COPD (Rennard et al 2001; Casaburi et al 2002) although the mechanism(s) of this effect is currently unknown. Possible anti-inflammatory effects of long-acting β_2 -agonists (Johnson and Rennard 2001) might explain the reduced frequency of exacerbations of COPD (Mahler et al 1999; Rennard et al 2001; Calverley, Pauwels, et al 2003). These bronchodilators do not seem to cause tachyphylaxis, namely rapid reduction in the intensity of the pharmacological effect due to continued or repeated administration, and are well tolerated. Although bronchodilator treatment in COPD is generally started with a single agent, the use bronchodilators in combination is suggested in the current guidelines as this strategy can result in improved bronchodilator and clinical effect (GICOPD 2001; Celli and McNee 2004). However, the interindividual variability of the bronchodilating effect can be high. The efficacy of combining either short or long-acting β_2 -agonists with anticholinergics (COMBIVENT 1994; van Noord et al 2000, 2006), anticholinergics and theophylline (Bleecker and Britt 1991; Bellia et al 2002), and all three classes of bronchodilators is known (Nishimura et al 1995). A fixed inhaled combination of albuterol and ipratropium is available.

High doses of nebulized bronchodilators are still widely prescribed for severe COPD. The British Thoracic Society (BTS) guidelines on nebulizer therapy (NPG 1997) recommend that a respiratory physician should evaluate the effectiveness of nebulizer therapy. Before trying chronic nebulizer therapy, it is advisable to evaluate the efficacy of high dose bronchodilator treatment delivered by metered dose inhaler (MDI) with a spacer. The administration of theophylline for stable COPD remains controversial. Theophylline causes bronchodilation in COPD (Murciano et al 1989; McKay et al 1993) with a variable effect on exercise tolerance and symptoms (Murciano et al 1984; Cooper et al 1987; Chrystyn 1988; Mulloy and McNicholas 1993). Theophylline has a slow onset of action and it is generally recommended for maintenance treatment, rather than for the rapid treatment of symptoms. In the major guidelines for the treatment of COPD, theophylline is considered a third line bronchodilator after inhaled anticholinergics and β_2 agonists (Barnes 2006). Nevertheless, theophylline is a useful treatment in patients with severe COPD as its withdrawal leads to significant clinical worsening of the disease (Kirsten DK 1993). The

most recent and largely selective phosphodiesterase inhibitors, such as inhibitors of phosphodiesterase type 4 isoenzyme, slightly improve lung function in COPD (Compton et al 2001) and reduce the frequency of exacerbations (Edelson et al 2001; Rabe et al 2005; Rennard et al 2006) (see below). However, further studies are needed to adequately evaluate the efficacy and tolerability of this new class of drugs.

Long-acting bronchodilators administered once or twice daily can improve symptoms to the same extent or more compared with chronic administration of short-acting bronchodilators. For this reason it is possible to consider the use of long-acting bronchodilators for the treatment of COPD patients requiring chronic treatment to improve symptoms. Theophylline may be recommended for patients with persistent symptoms instead of long-acting bronchodilator treatment. However, because of the disadvantages outlined above, administration of theophylline should be continued only if its efficacy on the symptoms has been demonstrated. The role of theophylline in the treatment of COPD is currently being re-evaluated based on important pharmacological evidence which has allowed the molecular mechanism of action of theophylline to be clarified (Barnes 2003).

Inhaled glucocorticoids are generally prescribed for COPD without demonstration of their effectiveness. However, COPD patients generally have no, or a negligible, response to glucocorticoids (Pauwels et al 1999; Vestbo et al 1999; Burge et al 2000; LHSRG 2000; RS 2003). Some patients may improve after glucocorticoid treatment, but it is likely that these patients have concomitant asthma (Barnes 2000). A two-week trial of oral glucocorticoids was proposed to identify patients with a documented spirometric response, assuming that an acute response is predictive of a chronic response (GISCOPD 2001). However, the oral administration of glucocorticoids for two weeks does not generally allow identification of those patients who will respond to inhaled glucocorticoids (Senderovitz et al 1999; Burge et al 2000, 2003). Therefore, a trial of glucocorticoids is not generally recommended for COPD (GISCOPD 2001), unless required to exclude asthma (Barnes 2000). Glucocorticoids do not reduce airway inflammation in COPD (Barnes 2000) and various long-term studies showed that glucocorticoids are not able to reduce the progression of COPD (Pauwels et al 1999; Vestbo et al 1999; Burge et al 2000; LHSRG 2000). For this reason, and taking into account the risk of systemic side effects, particularly at high doses, glucocorticoids should not generally be administered

for COPD (Barnes 2000), though they are recommended for the treatment of exacerbations. Furthermore, inhaled glucocorticoids are recommended for symptomatic COPD patients who have a documented spirometric response to these drugs or for patients with $FEV_1 \leq 50\%$ of the predicted value and frequent exacerbations (two or more per year), which require antibiotics or oral glucocorticoids, according to the GOLD guidelines (GISCOPD 2001). However, these recommendations are not universally agreed (Barnes 2000), as the effect of inhaled glucocorticoids at high doses on the frequency of exacerbations in patients with severe COPD is controversial (Paggiaro et al 1998; Burge et al 2000). Furthermore, the cost of glucocorticoids as well as their pharmacological profile, as discussed above, does not justify indiscriminate administration of inhaled glucocorticoids in COPD. Fixed combinations of inhaled glucocorticoids and long-acting β_2 -agonists, namely fluticasone–salmeterol (Dransfiel and Bailey 2004) and budesonide–formoterol, were approved for use in COPD in the US and other countries based on clinical trials showing their effectiveness for health status and exacerbations of COPD (Calverley, Boonsawat, et al 2003; Calverley, Pauwels, et al 2003; Szafranski et al 2003). However, there were conflicting results when the different combination therapies were compared with the mono-component alone (Nannini et al 2004). More studies to definitively establish the effects of combination therapy in a single inhaler are required, including double-dummy trials on the comparative effects with separate administration of the two drugs (Nannini et al 2004).

Other drugs

Vaccines

Vaccination can reduce severe complications and mortality from influenza in elderly patients, including those with COPD. Vaccination is recommended once in the autumn or, once in the autumn and once in the winter each year (Nichol et al 1994; Hak et al 1998). Pneumococcal vaccines have been used in COPD patients and can reduce complications of pneumonia in elderly patients, but there is no evidence to support its general use in COPD patients.

Antibiotics

Numerous large-scale controlled studies have shown that prophylactic antibiotics and chronic antibiotic administration have no effect on the frequency of exacerbations in COPD (MacNee and Calverley 2003). Prophylactic antibiotics are also ineffective in winter

(MacNee and Calverley 2003). Current available data does not support the effectiveness of prophylactic antibiotics against bacterial infections or exacerbations of COPD.

Mucolytic agents

Mucolytic agents such as ambroxol, erdosteine, carbocysteine, and iodinated glycerol produce a reduction in the frequency of exacerbations in chronic bronchitis compared with a placebo (Poole and Black 2000). Since these studies are of relatively short duration, between two to six months, and in patients with mild to moderate COPD ($FEV_1 > 50\%$ of the predicted value), the systematic administration of mucolytic drugs in COPD is not currently recommended.

Antioxidants

Oxidant stress plays an important role in the pathophysiology of COPD. Therefore, administration of antioxidant agents is an interesting treatment strategy. Although antioxidant and mucolytic drug N-acetylcysteine has been shown to reduce the frequency of exacerbations of COPD in most clinical trials (Grandjean et al 2000), a recent 3 year randomized placebo-controlled multicenter trial has shown that N-acetylcysteine is ineffective at prevention of deterioration in lung function and prevention of exacerbations in patients with COPD (Decramer et al 2005). On the basis of current data, N-acetylcysteine is not recommended for COPD (MacNee and Calverley). The details of various antioxidants trials are discussed elsewhere (Rahman 2006).

Drugs in phase III of clinical development

Phosphodiesterase-4 inhibitors

Selective inhibitors of phosphodiesterase (PDE) type 4 increase intracellular concentrations of cyclic AMP by inhibiting its breakdown with consequent airway smooth muscle relaxation and anti-inflammatory effects on effector cells involved in the pathophysiology of COPD (Lipworth 2005). PDE4 enzymes include at least four isoenzymes (PDE4A, PDE4B, PDE4C, and PDE4D) (Soderling and Beavo 2000). Inhibition of PDE4B is mainly responsible for the anti-inflammatory effects of PDE4 inhibitors, whereas inhibition of PDE4D causes nausea which is one of the main adverse effects of these drugs (Lipworth 2005). Cilomilast and roflumilast, the two main orally active PDE4 inhibitors, are in the late phase III of clinical development

for COPD (Lipworth 2005). Placebo-controlled studies for up to 6 months with cilomilast 15 mg twice daily and roflumilast 500 mg once daily have shown small, although significant, improvements in lung function tests in patients with COPD (Compton et al 2001; Rabe et al 2005). PDE4 inhibitors also reduce the rate of COPD exacerbations compared with placebo (Rabe et al 2005; Rennard et al 2006). The effect of PDE4 inhibitors on health status in patients with COPD is variable possibly due to differences in the duration of treatment (Compton et al 2001; Rabe et al 2005; Rennard et al 2006). Cilomilast at a dose of 15 mg twice daily for 12 weeks reduces CD4+ T-lymphocyte subsets and CD68+ macrophages in bronchial biopsies from patients with COPD (Gamble et al 2003). However, whether these changes in airway inflammation are related to clinical outcomes in patients with COPD is unknown (Lipworth 2005). The main adverse effects of PDE4 inhibitors are nausea, diarrhea, and abdominal pain (Lipworth 2005). Roflumilast is more tolerated than cilomilast as it has similar selectivity for PDE4 isoenzymes, whereas cilomilast is 10 times more selective for PDE4D than other isoenzymes (Manning et al 1999; Hatzelmann and Schudt 2001). Long-term studies are required to definitively establish the effects of PDE4 inhibitors on clinical outcomes, including lung function, exacerbation rate, and health status in patients with COPD.

Treatment of exacerbations of COPD

According to a recent definition, exacerbations of COPD are “a variation in symptoms above the normal day to day variation which causes a change in a patient’s medication” (Rodriguez-Roisin 2000). Exacerbations of COPD worsen general health status (Seemungal et al 1998) and are considerably expensive. The number of exacerbations is related to disease severity. Patients with moderate to severe COPD have one or two exacerbations per year (Seemungal et al 1998; Burge et al 2000). Many factors determine the type of treatment used and where the treatment is carried out, for example, in an outpatient or hospital setting.

The severity of the exacerbations is related to the severity of the disease. In patients with mild COPD, exacerbations are associated with increased breathlessness accompanied by cough and sputum production. They may often be managed out of hospital. Exacerbations of severe COPD are often associated with respiratory failure which may be fatal and require hospital admission on a general ward or intensive care unit. Exacerbations are caused by bacterial

or viral infections in around 50% of cases (Monso et al 1995; Soler et al 1998; Seemungal et al 2000). Other factors such as air pollution and temperature may cause exacerbations (MacNee 2002). However, it is not possible to identify a cause in about one third of exacerbations of COPD (Connors et al 1996). One of the main problems is the decision to treat exacerbations of COPD at home or in hospital. This decision is influenced by the severity of symptoms, the severity of COPD, and whether hospital admission is required. Recent trials have shown that about 30% of patients admitted to hospital with exacerbations of COPD could be adequately treated at home with immediate or early discharge and nurse-led home care (Skwarska et al 2000; Cotton et al 2000; Davies et al 1999, 2000). Patients prefer this form of treatment, which has been widely adapted to facilitate the discharge of those patients initially requiring hospitalization (Cotton et al 2000; Ojoo et al 2002). However, a clinical trial showed that home care did not improve the health of the patients whilst increasing costs compared with admission to hospital (Shepperd, Harwood, Gray, et al 1998; Shepperd, Harwood, Jenkinson, et al 1998).

Home treatment

The algorithm shown in Figure 3, which is based on a stepwise therapeutic approach (Sachs 1981; ATS 1995; Siafakas et al 1995; Celli 1996; Shepperd, Harwood, Jenkinson, et al 1998), may be used in the home treatment of exacerbations of COPD using bronchodilators, if necessary delivered by nebulizer, or antibiotics if symptoms indicate a bacterial infection, and oral glucocorticoids in moderate to severe exacerbations. The dose and/or frequency of bronchodilator delivery must be increased or bronchodilator treatment must be started if these drugs have not been used previously. Administration of high doses of antimuscarinics on demand delivered for a number of days using a nebulizer may be useful, even though chronic nebulizer treatment is not generally recommended after an exacerbation (GICOPD 2001). Systemic glucocorticoids are effective for exacerbations of COPD as they facilitate clinical improvement and lung function (Thompson et al 1996; Niewoehner et al 1999; Cotton et al 2000) and are recommended for patients with moderate to severe exacerbations of COPD when the baseline FEV₁ is less than 50% of the predicted value (GICOPD 2001). The optimum dose and duration of treatment is not known, but administration of oral prednisolone at 40mg per day for ten days is generally effective (GICOPD 2001). Nebulized budesonide is as effective as oral glucocorticoids in

improving lung function. However, it is not clear whether the increased costs of inhaled glucocorticoids are justified in all cases (Maltais et al 2002). Antibiotic treatment, which does not generally require parenteral administration, is recommended if two or more of the following symptoms are present: increasing dyspnoea, increasing sputum purulence, or increasing sputum volume (Anthonisen et al 1987). Antibiotics should be chosen which are effective against *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. These are the bacteria that most frequently cause exacerbations of COPD. However, the choice of antibiotics must be based on the antibiogram (GICOPD 2001).

Hospital treatment

The criteria for necessary hospital treatment, whether during admission to the emergency department, or during hospitalization, for exacerbations of COPD are described

in the GOLD guidelines (GICOPD 2001). Hospital treatment is increasingly focused on the management of lung function and associated complications, particularly considering the increased number of early discharges (MacNee and Calverley 2003). Firstly, it is necessary to establish whether the exacerbation of COPD may be life-threatening and if this is the case the patients must be admitted to intensive care. The risk of mortality from exacerbations of COPD is connected with the level of respiratory acidosis, the presence of concomitant diseases, and the need for assisted ventilation (Connors et al 1996). In the absence of these characteristics, the risk of mortality is low, even though patients with severe COPD require hospitalization (GICOPD 2001). In these cases the effectiveness of home treatment is poor (Shepperd, Harwood, Gray, et al 1998). However, the results are better if home treatment follows a careful assessment in the emergency department and is combined with adequate doctor- or nurse-administered home care (Gravil et al 1998).

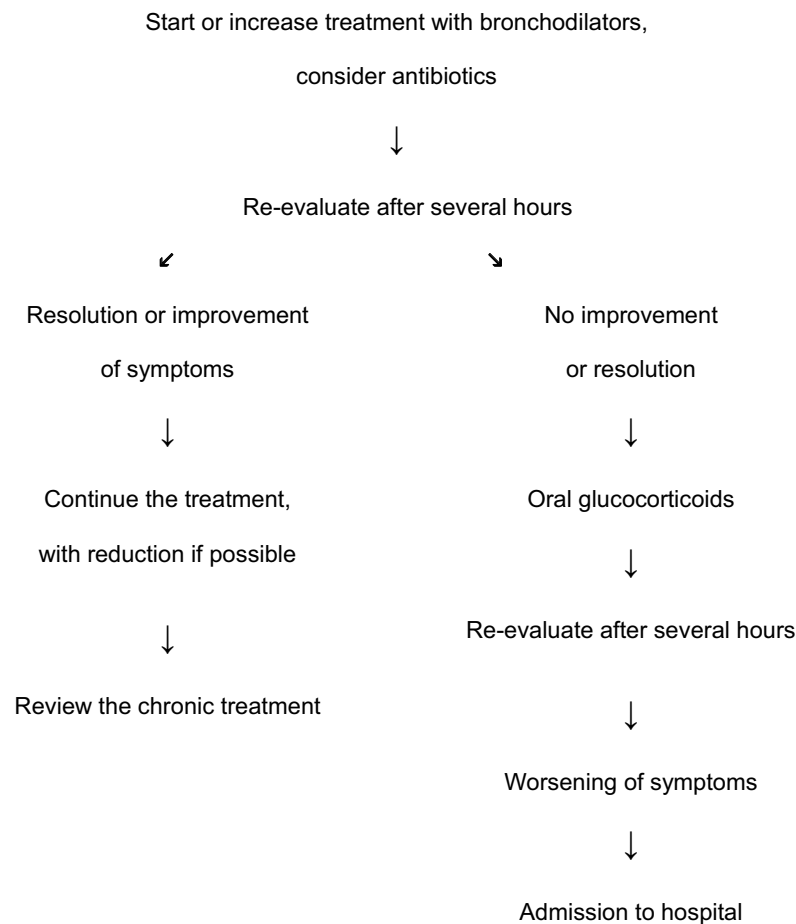


Figure 3 Algorithm for the home treatment of an exacerbation of COPD (adapted from Global Initiative for Chronic Obstructive Lung Disease. 2001. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. National Institutes of Health. National Heart, Lung, and Blood Institute. Publication number 2701).

Controlled oxygen therapy is the cornerstone of hospital treatment of exacerbations of COPD (GICOPD 2001). It is relatively easy to achieve adequate oxygenation ($\text{PaO}_2 > 60 \text{ mmHg}$ or $\text{SaO}_2 > 90\%$) in uncomplicated exacerbations, but CO_2 retention can occur (GICOPD 2001). β_2 -agonists are the main bronchodilators used for the treatment of exacerbations of COPD (Siafakas et al 1995; Celli 1996; BTS 1997). If rapid bronchodilation does not occur with these drugs, an antimuscarinic agent may be administered, even if the effectiveness of this combination is controversial (Fernandez et al 1994; Moayyedi et al 1995). The role of theophylline in the treatment of exacerbations of COPD is also controversial (GICOPD 2001). Theophylline leads to modest improvements in lung function without gas exchange deterioration (Barbera et al 1992; Mahon et al 1999). Administration of intravenous theophylline can be considered in more severe exacerbations (GICOPD 2001) although the available data do not support the use of methylxanthines for the treatment of exacerbations of COPD (Barr et al 2003). However, this requires close monitoring of the plasma concentrations to avoid the occurrence of dose-dependent toxic effects (Lloberes et al 1988; Emerman et al 1990; Barbera et al 1992). Oral or intravenous glucocorticoids are recommended with bronchodilator therapy and, if necessary, antibiotics and oxygen therapy, for treatment in hospital of exacerbations of COPD (Thompson et al 1996; Davies et al 1999; Niewoehner et al 1999; GICOPD 2001). The optimum dose of glucocorticoids is not known, but high doses increase the risk of significant side effects. Generally 30 mg to 40 mg of oral prednisolone is administered for 10 to 14 days (GICOPD 2001). Prolonged treatment does not improve efficacy, while increasing the risk of side effects. Antibiotics are only effective when exacerbations also occur with sputum purulence and increased sputum volume and/or fever, indicating a bacterial infection (Anthonisen et al 1987). Antibiotics must be effective against *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. These are the bacterial microorganisms most frequently involved in exacerbations of COPD. However, the choice of antibiotics must be based on the antibiogram. Toxicity due to excessive oxygen therapy in the emergency department is still a prevalent problem which could be resolved by increasing patient awareness of the risk (Plant et al 2000a). In cases of severe exacerbations of COPD (stage III) mechanical ventilation is required which may be invasive (conventional) or non-invasive with the aim of reducing morbidity and mortality and improving symptoms.

Non-invasive positive pressure ventilation (NIPPV) is an effective alternative to conventional mechanical ventilation in the intensive care unit and is even applicable in the general ward with specialized nursing staff (Brochard et al 1995; Plant et al 2000a). NIPPV reduces patient morbidity and length of stay in hospital by preventing the onset of nosocomial pneumonia, but it is less effective than intermittent positive pressure ventilation in patients with a pH persistently < 7.30 (Plant et al 2000b).

Conclusions

Pharmacological treatment of COPD is currently symptomatic and is based on inhaled bronchodilators such as anticholinergics, selective β_2 -adrenergic agonists and theophylline. In the absence of proven efficacy and due to higher costs and side effects, glucocorticoids are not generally recommended for stable COPD, though they are effective in the treatment of exacerbations. In the absence of drugs which reduce progressive decline in lung function, which is the hallmark of this disease, cessation of cigarette smoking, the main risk factor for COPD, is the most effective measure. Numerous studies are being carried out to define the pathophysiology of COPD, about which still relatively little is known. It is hoped that these studies will allow new and effective drugs to be discovered and developed, as the current pharmacological treatment of COPD is inadequate.

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