

## COPD

— *pharmacological management*

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*Pharmacological treatment of chronic obstructive pulmonary disease, while not providing a cure, is used to manage the symptoms and maintain quality of life. This article reviews the drug treatment available for the disease*

*Computer-enhanced image of a resin cast of the airways in the lungs, the target for drug therapy in COPD*

**C**hronic obstructive pulmonary disease (COPD) has a major impact on the UK health system. Although there is no cure for COPD, various options are available for its management. Appropriate management of COPD can significantly affect symptoms and quality of life, even for patients with severe disease.

Recent trials have been published with grade A or B evidence levels (eg, randomised controlled clinical trials) which have clarified the role of some of the newer agents available for symptomatic relief, improving quality of life and preventing exacerbations. Furthermore, new evidence-based guidelines commissioned by the National Institute for Clinical Excellence (NICE) have been published this year on the management of COPD.

This article provides an overview of the approaches to managing COPD and gives an insight to potential pharmacological developments that might be seen in the future. A multidisciplinary approach to managing COPD is needed and the pharmacist

has a vital role. A number of pharmaceutical care issues are addressed and the roles that pharmacists may have in improving the quality of care for patients suffering with COPD are discussed.

#### — DRUG TREATMENTS

**D**rug therapy is used to prevent and control symptoms, reduce the frequency and severity of exacerbations, improve health status and improve exercise tolerance.<sup>1</sup> The overall approach to managing COPD should be characterised by an individualised assessment of disease severity and response to various treatments. Treatments should be monitored closely and adjusted accordingly. Traditionally, the response to bronchodilators and corticosteroids was assessed by reversibility testing using a spirometer. A positive response implied that the patient would benefit from the long-term use of that particular drug and might have a better prognosis. While spirometry remains essential for confirming the diagnosis of airflow obstruction, reversibility testing is no longer routinely recommended to guide drug therapy. The effectiveness of therapy should be assessed by a variety of measures, not just lung function.<sup>1</sup> Patients' symptoms, activities of daily living, exercise tolerance and exacerbation rate should be measured. If a treatment has no impact on these symptoms then the medicine should

be reviewed with the aim of stopping the therapy. Panel 1 (p368) indicates the type of question that can be used to help assess the effectiveness of a medicine in a patient with COPD.<sup>2</sup>

#### — BRONCHODILATORS

**A**lthough COPD is characterised by irreversible airflow obstruction, many patients show clinical benefits from bronchodilators.<sup>1</sup> Bronchodilator drugs alleviate airway smooth muscle tone and increase airway calibre. Bronchodilators alleviate breathlessness through their direct effect on the airway, but these drugs also lead to a reduction in pulmonary hyperinflation, increase mucociliary clearance and improve respiratory muscle function. This probably explains why clinical benefits may be seen without clear changes in the patient's lung function. There are three classes of bronchodilators:

- Beta-2-agonists (short-acting and long-acting)
- Anticholinergics (short-acting and long-acting)
- Methylxanthines

The majority of COPD patients will require a short-acting bronchodilator. The long-acting bronchodilators should be used in those patients who remain symptomatic despite treatment with a combination of

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## Panel 1: Questions to assess effectiveness of medication

- Has your treatment made a difference to you?
- Is your breathing easier in any way?
- Can you do some things now that you could not do at all before the treatment, or do you do the same things but faster?
- Can you do the same things as before but are now less breathless when you do them?
- Has your sleep improved?

both short-acting bronchodilators. Patients who remain symptomatic should have their inhaled treatment stepped-up as shown in Figure 1 (p370).<sup>1</sup> Long-acting bronchodilators should also be used in patients who have two or more exacerbations per year.<sup>1</sup>

### — SHORT-ACTING BETA-2-AGONISTS

Short-acting beta-2-agonists, such as salbutamol and terbutaline, are the most widely used bronchodilators for COPD. They relax airway smooth muscle and reduce breathlessness. The onset of action is slower than in patients with asthma. They act at beta-2-adrenergic receptors on airway smooth muscle, mimicking the effects of the sympathetic nervous system. They relax airway smooth muscle, enhance mucociliary clearance and decrease vascular permeability (part of the inflammatory response). Inhalation of beta-2-agonists is more effective than oral administration in producing bronchodilation, giving a more rapid onset of action and fewer side effects. There is no evidence that any one beta-2-agonist is more effective than any other.

Adverse effects of beta-2-agonists include tremor, tachycardia and increased anxiety, but these effects are minimal when the drug is taken by inhalation and at the recommended dose. The side effect to benefit ratio is such that there is little point in giving more than 1mg salbutamol in patients with COPD.<sup>3</sup> Hypokalaemia is observed following inhaled and systemic administration of beta-2-agonists. This is mediated by the uptake of potassium ions in skeletal muscle. The change in plasma concentration of potassium ions is minimal under normal therapeutic doses.

Beta-2-agonists can reduce arterial oxygen tension as a consequence of ventilation or perfusion mismatching (good perfusion, as a result of pulmonary vasodilatation, with poor ventilation, leads to a drop in the partial pressure of oxygen). Such effects can present problems in individuals who are

already severely hypoxemic (low concentration of oxygen in arterial blood) and may therefore require oxygen supplementation. In practice these patients may require oxygen delivered via nasal cannulae during nebulisation of beta-2-agonist. Side effects of beta-2-agonists are listed in Panel 2 (p370).

Beta-2-agonists are available in a wide variety of formulations: metered-dose inhalers, nebuliser solutions, oral liquids, tablets and powders for inhalation.

### — SHORT-ACTING ANTICHOLINERGICS

Short-acting anticholinergics, for example ipratropium (Atrovent), act by reducing reflex cholinergic bronchoconstriction and vagal airway tone. They also reduce airway mucus secretion. The onset of action is slower than with beta-2-agonists (approximately 30 minutes) but the bronchodilation is more sustained (up to eight hours) and at least as effective.<sup>4,5</sup> In practice many COPD patients benefit from anticholinergics. Side effects which may be seen include, dry mouth, blurred vision and paradoxical bronchospasm. If ipratropium is being nebulised, the mask must be fitted carefully or ideally a mouthpiece used to avoid the aerosol coming into contact with the eyes, which could cause glaucoma. Anticholinergics have no effect on pulmonary vessels, and therefore there is no fall in the partial pressure of oxygen, as may sometimes be seen with beta-2-agonists and methylxanthines.

### — LONG-ACTING BETA-2-AGONISTS

The advantage of the long-acting bronchodilators is that they produce a sustained relaxation of the airway for approximately 12 hours. The degree of bronchodilation is similar to a short-acting beta-2-agonists. There are two long-acting beta-2-agonists available in the UK: formoterol (Oxis) and salmeterol (Serevent). The drugs have slightly different molecular structures producing altered onset and duration of action. Salmeterol has a slower onset of action. Both drugs produce small improvements in lung function by increasing the forced expiratory volume in one second (FEV<sub>1</sub>), but studies have not shown consistent effects in reducing exacerbation rates and improving quality of life of COPD patients.<sup>6</sup> Long-acting beta-2-agonists are more expensive than short-acting ones, but in patients who respond they are more convenient.

Side effects from long-acting beta-2-agonists are the same as from the short-acting agents and are similarly few when the inhaled route is used and at recommended doses.

## Panel 2: Side-effects of beta-2-agonists

- Muscle tremor (direct effect on skeletal muscle beta-2-receptors)
- Tachycardia (direct effect on atrial beta-2-receptors, reflex effect from increased vasodilatation via beta-2-receptors)
- Hypokalaemia (direct effect on skeletal muscle uptake of potassium ions via beta-2-receptors)
- Restlessness
- Hypoxaemia (increased V/Q [ventilation/blood flow] mismatch due to pulmonary vasodilatation)

### LONG-ACTING ANTICHOLINERGICS

A longer acting anticholinergic, tiotropium (Spiriva), has recently become available. Tiotropium has a duration of action in excess of 24 hours and can be administered once a day.<sup>7,8</sup> It has pharmacokinetic advantages<sup>9,10</sup> over the short-acting anticholinergics producing improvements in lung function and health status, reducing breathlessness and improving exercise tolerance. Tiotropium is well tolerated. The most common side effect in clinical trials was dry mouth, seen in 9 to 15 per cent of the participants, although this was not statistically significantly greater than results with ipratropium.<sup>11</sup> Tiotropium is available in a new type of inhaler device; the "HandiHaler". This is a dry powder device and has the advantage that it can be used at low inspiratory flow rates, which is ideal for patients with COPD. The drug is formulated into a capsule of 18µg and is inhaled via the "HandiHaler" once a day. It is important that patients are instructed how to use this new device.

### METHYLXANTHINES

The two methylxanthine drugs available in the UK are theophylline and aminophylline. They have a small bronchodilator effect in COPD and may have anti-inflammatory activity although the latter has yet to be fully assessed.<sup>12,13</sup> Both may also increase diaphragmatic strength in patients with COPD and have effects on mucociliary clearance. However, due to the potential toxicity and significant interactions with other drugs, methylxanthines are recommended for use when other treatments have failed or when a patient remains symptomatic despite optimal bronchodilator therapy.<sup>1</sup> They can be useful in certain cases to improve compliance, as both are available as oral formulations. To reduce the adverse effects, such as nausea, headaches and gas-

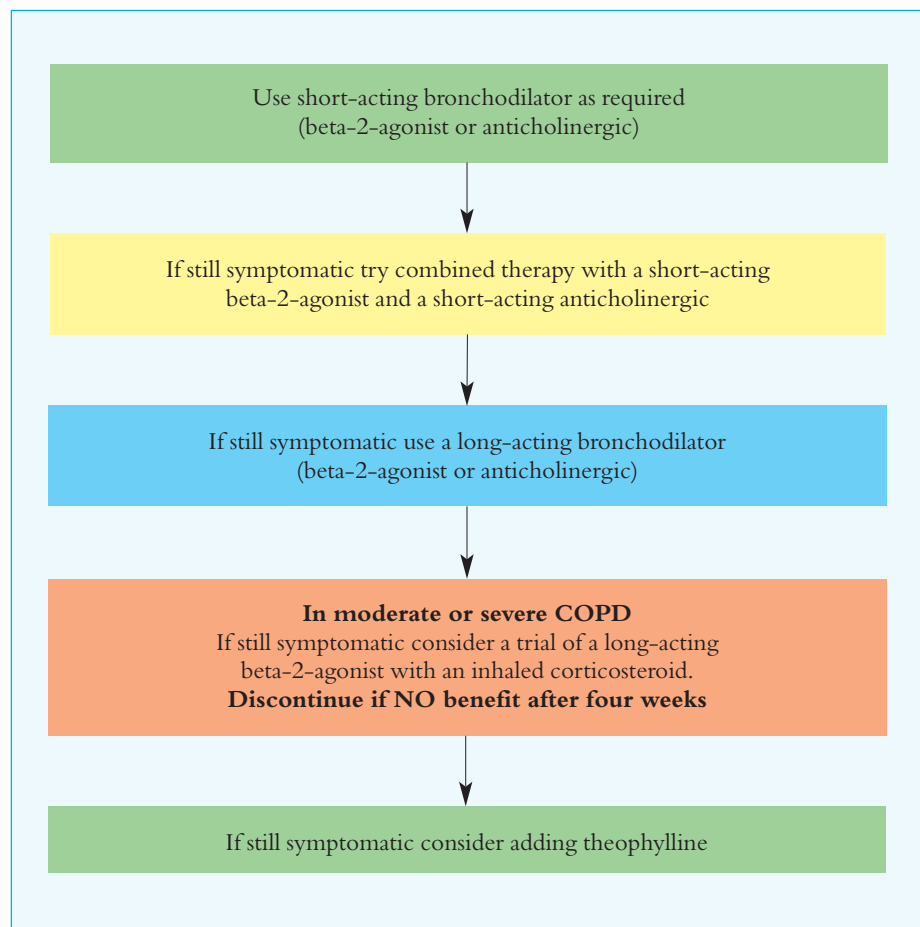


Figure 1: Algorithm for the pharmacological management of breathlessness and exercise limitation

trointestinal reflux, a low dose of oral theophylline should be introduced. The dose should then be gradually increased according to symptoms and plasma levels. Plasma levels should be monitored after initiating therapy. For most patients a measurement of plasma theophylline concentrations eight to 10 hours following a single oral dose will be sufficient to predict maintenance requirements and a repeat measurement one to two weeks later will confirm that the plasma concentration is in the therapeutic range.<sup>14</sup> Thereafter, monitoring is not necessary unless there has been a change in concomitant medication or the patient's condition that would lead to altered theophylline clearance. The clearance of the methylxanthines is affected by many factors, including cigarette smoking, viral pneumonia, heart failure and concurrent drug treatment (Panel 3, p372). Caution is particularly required in prescribing for the elderly population because of differences in pharmacokinetics, the increased likelihood of co-morbidities and the use of other medicines.

### INHALED CORTICOSTEROIDS

Although inflammatory changes are present in the airways of COPD patients, the inflammation is mediated by neutrophils, which are relatively insensitive to

the effects of steroids. Even high doses of corticosteroids do not reduce the inflammation in stable COPD patients. This is different in asthma patients, who have inflammation mediated by eosinophils, which respond extremely well to steroids.

The role of inhaled steroids in stable COPD is controversial and has been the subject of four recent large trials.<sup>15-18</sup> All used changes in the rate of decline in lung function as the primary end point and showed no benefit. However, inhaled steroids appear to reduce exacerbations in patients with severe disease.<sup>17-19</sup> Hence, the principal indication for the use of inhaled corticosteroids is in patients with moderate or severe COPD who are experiencing two or more exacerbations per year. However, evidence from studies suggests that adding inhaled steroids to long-acting beta-2-agonists can also reduce breathlessness. This combination may be beneficial in patients who are still breathless despite monotherapy with long acting beta-2-agonists.<sup>20-22</sup> The patient must be monitored carefully for improvements in symptoms, activities of daily living and exercise tolerance. The inhaled corticosteroid should be discontinued if there is no improvement in the patient's breathlessness after four weeks.

None of the inhaled corticosteroids currently available is licensed for use alone in the treatment of COPD. Yet it has been

### Panel 3: Examples of factors affecting clearance of methylxanthines

#### Increased clearance (increase dose)

Enzyme induction (eg, rifampicin, ethanol, phenobarbitone)

Smoking (tobacco, marijuana)

Childhood

High protein, low carbohydrate diet

#### Decreased clearance (decrease dose)

Enzyme inhibition (eg, cimetidine, ciprofloxacin, allopurinol)

Congestive heart failure

Liver disease

Pneumonia

reported that 70 per cent of patients with COPD are prescribed an inhaled corticosteroid and 5 per cent are taking oral steroids. This reflects the fact that many COPD patients are treated as asthma sufferers.

#### TREATMENT OF ACUTE EXACERBATIONS

Exacerbations are a major cause of hospital admissions for COPD. Therefore efforts to reduce the number of exacerbations of COPD may lower the costs associated with hospital admissions. An exacerbation is defined as a sustained worsening of the patient's symptoms from his or her usual stable state that is beyond normal day-to-day variations and is acute in onset.<sup>1</sup> Panel 4 lists interventions to reduce exacerbations. The pharmacological management of an acute exacerbation of COPD is outlined in Figure 2 (p375).

**Corticosteroids** Studies using inhaled corticosteroids in patients with mild COPD showed no effect on exacerbation rates. The reported benefit appears in patients with more severe COPD (mean FEV<sub>1</sub> of 50 per cent predicted).<sup>17-19</sup> In this cohort of patients exacerbation rates were reduced by 25 per cent from 1.32 per year on placebo to 0.99 per year on inhaled corticosteroid.<sup>18</sup> It is therefore recommended that inhaled corticosteroids are prescribed for patients with an FEV<sub>1</sub> of less than or equal to 50 per cent of predicted who are having two or more exacerbations requiring treatment with antibiotics or oral corticosteroids in a 12-month period.<sup>1</sup>

There is a potential risk of patients developing osteoporosis and other side effects from treatment with high dosages of inhaled corticosteroids<sup>23</sup> so it is important that the prescribing of them is limited to the above group of patients or those who gain symptomatic benefit.

Routine use of oral corticosteroids is not recommended but may be necessary in those patients with severe disease who are unable to withdraw the oral steroids following an exacerbation. In this case the dose should be

kept to a minimum and any patient over the age of 65 years prescribed an osteoporosis prophylactic agent.

#### SMOKING CESSATION

Stopping smoking can reduce the rate of decline in lung function seen in most patients with COPD who smoke and can improve survival rate.<sup>24,25</sup> It does not restore already lost lung function. Lung function falls continuously and smoothly over an individual's life, with the rate of loss accelerating slightly with age. Non-smokers and non-susceptible smokers lose FEV<sub>1</sub> slowly and almost never develop clinically significant airflow obstruction. By sharp contrast, susceptible smokers develop various degrees of airflow obstruction, which, ultimately, become disabling or even fatal. In these individuals, stopping smoking will never restore the lost FEV<sub>1</sub>, but the subsequent rate of loss may revert to normal. Among smokers who have already developed moderate obstruction, the effect of quitting at age 45 can make the difference between a normal lifespan and premature death. Screening smokers' lung function in early middle age, therefore, could help to prevent severe or fatal COPD if those with reduced function could be persuaded to stop smoking.

Symptoms of cough and sputum production are markedly reduced when the patient stops smoking. Smoking cessation advice is an essential part of the management of COPD and should be offered to patients at every opportunity. The most successful smoking cessation interventions are those that include advice and support along with pharmacological intervention.<sup>26</sup> Nicotine replacement therapy (NRT) and bupropion are recommended for smokers who have expressed a desire to quit smoking. They should be prescribed only when the smoker has made a commitment to stop smoking on or before a particular date.<sup>26</sup>

There is currently no evidence to support one form of NRT over another. We should therefore discuss with the patient the best form of NRT to suit them. In terms of percentages of smokers quitting, the average

### Panel 4: Interventions to reduce exacerbations

- All patients should be encouraged to have annual influenza and pneumococcal vaccinations
- Long-acting bronchodilators should be used in patients who have two or more exacerbations per year
- Patients should be instructed to respond appropriately to the first sign of an exacerbation. Starting courses of antibiotics or oral steroids that they have been given to keep at home or adjusting their bronchodilator therapy may lead to reduced hospital admissions
- Inhaled corticosteroids
- Mucolytic agents
- Pulmonary rehabilitation

over all trials looking at NRT shows that about 10 per cent of patients had not smoked for the 12 months following placebo treatment and about 17 per cent had not smoked following NRT. Overall results from clinical trials with bupropion showed that 9 per cent of patients had not smoked 12 months after placebo treatment and about 19 per cent had not smoked following bupropion therapy. There have been only two head-to-head studies comparing bupropion and NRT. The first study, which was a double-blind, double-dummy, randomised, placebo-controlled trial, compared bupropion with an NRT patch. The odds ratio at 12 months for continuous abstinence was 2.07 (95 per cent confidence interval 1.22-3.53) in favour of bupropion.<sup>26</sup> The second study, an open-label, non-placebo, randomised controlled trial, compared bupropion 300mg daily with NRT 4mg gum. There was no significant difference between the groups in quit rates at 12 months.<sup>26</sup>

The community pharmacist in particular is in a key position to support smoking cessation in both early and late disease. Community pharmacists may notice that patients are presenting more frequently at the pharmacy for cough medicines to treat their smoker's cough or collect prescriptions for repeated courses of antibiotics. Early identification of these patients may facilitate appropriate disease management and lifestyle changes before the end-stage of the illness when disability is substantial. Hospital pharmacists can also influence their patients smoking habits by providing advice on smoking cessation. The fact the patient has been admitted to hospital may give them the motivational incentive required to quit smoking. Even brief advice lasting about three minutes had been shown to increase quit rates.<sup>27</sup>

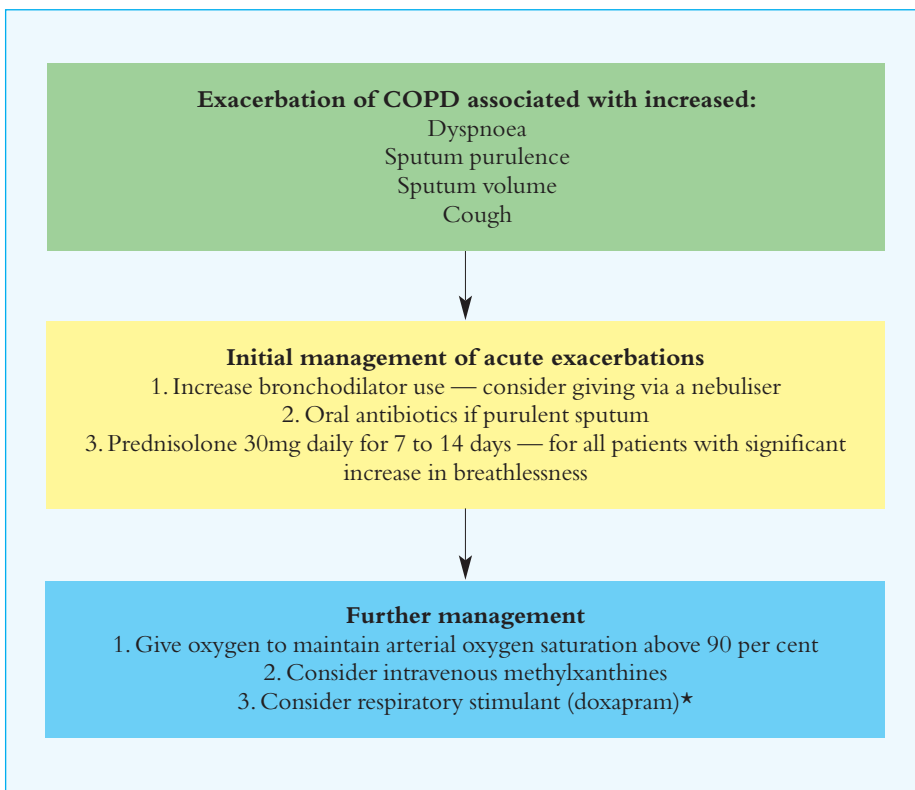


Figure 2: The pharmacological management of an acute exacerbation of COPD. \* It is recommended that doxapram is used only when non-invasive ventilation is either unavailable or considered inappropriate

### Panel 5: Future drugs<sup>29</sup>

Investigational drug	Potential mode of action
Leukotriene receptor antagonists, especially those affecting LTB <sub>4</sub>	Inhibit neutrophil chemotaxis into the airway
5-Lipoxygenase inhibitors (eg, zileuton)	Inhibit the production of LTB <sub>4</sub>
Phosphodiesterase-4 inhibitors (PDE4)	Reduce the activity of neutrophils
Colchicine	Inhibits neutrophil activity and reduces neutrophil elastase activity
Macrolide antibiotics, such as erythromycin	Neutrophil modifying effects independent of their antibiotic action
Angiotension 2 receptor antagonists, eg, losartan	May reduce hypoxic pulmonary vasoconstriction and may prevent the progression of pulmonary hypertension and cor pulmonale
Tachykinin antagonists	Inhibit hypersecretion of mucus

### Panel 6: Inhalation devices

- Metered-dose inhalers
- Spacers
- Breath-actuated devices
- Dry-powder devices
- Nebulisers

### — OXYGEN TREATMENT

Severe COPD leads to chronic hypoxia and an associated decline in health and prognosis. If left untreated the five year survival is less than 50 per cent.<sup>1</sup> The administration of supplemental oxygen has been shown to prolong life in COPD. This is discussed in more detail in the accompanying article (pp 359–64).

The provision of oxygen to patients is currently under review by the Department of Health and guidance will be offered shortly on the implementation of the new system.

### — MUCOLYTICS

Many patients with COPD cough up sputum. Mucolytics are believed to increase the expectoration of sputum by reducing its viscosity. Oral mucolytics were removed from the so called “black” list of the Drug Tariff from 1 February 2003 and can now be prescribed. Carbocysteine (Mucodyne) is available in the UK and should be considered in patients with a chronic cough producing sputum. A trial of mucolytic therapy should be given for one month. During this time patients should monitor the quantity of sputum production, sputum colour, ease of expectoration and amount of coughing. Therapy should only be continued after the initial month if the patient reports improvement in their cough and sputum production or expectoration and is experiencing no unacceptable side effects.<sup>28</sup>

There is no evidence to support the use of anti-tussive therapy in COPD and these preparations are not recommended.

### — NEW TREATMENTS

Most of the drugs currently used to treat COPD were originally developed for use in asthma. Increased interest in COPD over the past decade has led to the development of molecules specifically to treat this disease. A number of anti-inflammatory drugs and specific mediator antagonists are in development. In addition, drugs that reduce mucus secretion or improve mucociliary clearance are under investigation. Further information is presented in Panel 5.

### — DRUG DELIVERY

Many of the drugs used to manage COPD are delivered by inhalation. This is the preferred route because smaller doses of the drugs are needed, inhaled therapy works more quickly and the drug is delivered directly to the site of action (the airways). The devices used to deliver the drugs to the lungs (listed in Panel 6) are in many ways as important as the drugs themselves. The effectiveness of the therapy will be reduced if the patient is unable to use the device correctly. If a faulty technique cannot be remedied easily, the patient should switch to another device. Most patients, whatever their age, are able to acquire and maintain adequate inhaler technique as long as adequate instruction is given. Regular assessment and reinstruction is therefore essential. The

pharmacist should provide patient education and training on drug delivery in conjunction with other members of the multidisciplinary team.

Overall the metered-dose inhalers and spacers are the cheapest and the most versatile delivery systems but many patients do not always use the spacers when they should. Whichever device is chosen it must be acceptable to the patient and deliver the desired treatment easily, reliably and consistently.

Most patients achieve maximum possible bronchodilation with drugs administered by conventional inhalers, and nebulisers offer little additional benefit. However, a few patients with severe disease will benefit from high doses of bronchodilator treatment, which are best delivered by a nebuliser. Nebulisers are popular with patients because many patients derive subjective benefit from the cooling facial breeze, which helps to reduce the sensation of breathlessness. Nebulisers should only be used in patients after full assessment by a respiratory physician who can weigh up the potential benefits to the patient with the associated high costs and risks. Nebulisers should not be continued to be prescribed without assessing and confirming that one or more of the following occurs: a reduction in symptoms, an increase in the ability to undertake activities of daily living, an increase in exercise capacity or an improvement in lung function.

## RATIONALISATION OF THERAPY

Over a 12-month period, each COPD patient receives an average of 13.4 prescriptions.<sup>1</sup> Patients with COPD are therefore expected to manage a large number of medicines. As previously mentioned, patients should be assessed individually and treatments closely monitored and adjusted. Pharmacists are in an ideal position to take on this monitoring role to ensure appropriate and optimal patient care. Reduction of therapy once symptom control has been achieved is not normally possible in COPD. Further deterioration of lung function usually requires the progressive introduction of more treatments. However it is important to review the patient's medication to ensure that all medicines are appropriate according to the guidelines and are efficacious.

COPD is a common and important disease causing considerable morbidity. The total management of COPD is a challenge for all involved. Identifying patients with early stages of COPD, reducing the risk factors for developing COPD, such as smoking cessation, and managing the disease are potential roles for the pharmacist in the pharmaceutical care of the patient with COPD.

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