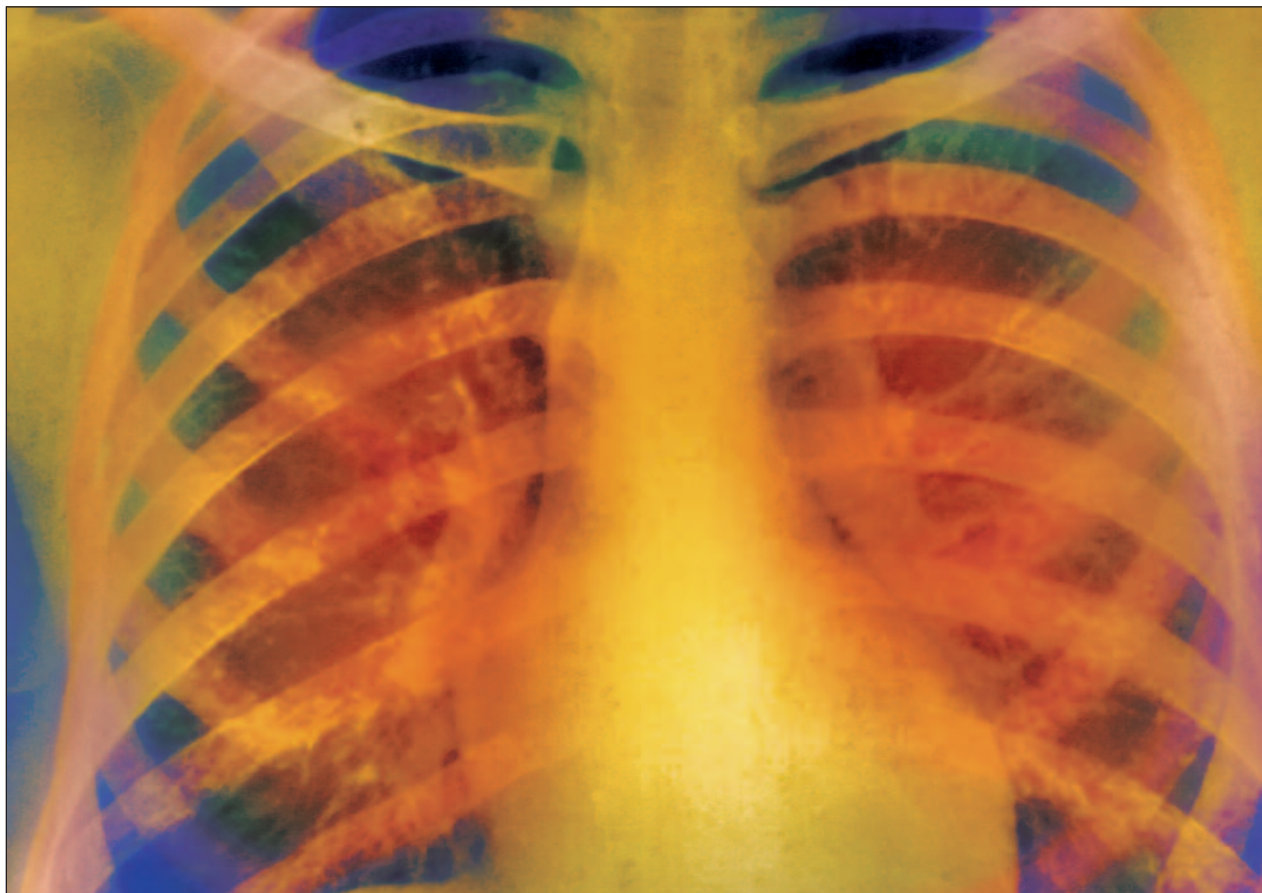


# Treatment options in chronic obstructive pulmonary disease

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**Management of chronic obstructive pulmonary disease requires a true multidisciplinary approach, and therapies with a strong evidence base can bring benefits to patients. Our Drug review considers the available treatments and their efficacy, followed by sources of further information.**

Over the last 15 years there has been a slow but steady transformation in the outlook for patients suffering from chronic obstructive pulmonary disease (COPD). From previous nihilism, management has been transformed using a variety of pharmacological

and nonpharmacological interventions. It is increasingly recognised that optimum management involves multiple interventions, which in the main produce a small but significant additive benefit to the individual.

Greater emphasis has been placed on patient-centred outcomes (such as functional capacity, reduction of exacerbations, activity and quality of life) instead of the traditional emphasis on changes in measures of lung function. This is welcome, not least because it recognises the profound effect that this disease has on an individual's life, and is pertinent considering the health costs associated with the disease.

COPD is predicted to be the fourth most important disability-producing illness by 2020 and continues to present a huge burden to both primary and secondary care.<sup>1</sup> Management has undoubtedly been aided by the pro-



CPD questions available for this article. See page 25

duction of various guidelines, including the international, annually updated Global initiative for Obstructive Lung Disease (GOLD) guideline<sup>2</sup> and, of particular importance to UK practitioners, the National Institute for Health and Clinical Excellence (NICE)/British Thoracic Society (BTS)/Scottish Intercollegiate Guidelines Network (SIGN) guideline. The latter is currently being revised and due for publication in 2010.

### **Making a diagnosis**

COPD is characterised by cough and phlegm production (chronic bronchitis) and exertional breathlessness (emphysema) with the chronic symptoms periodically punctuated by exacerbations, usually infective in nature. Breathlessness tends to be chronically progressive and is often accompanied by wheezing. Clinical signs are usually unhelpful and, although variation in peak flow can sometimes play a role in long-term management, the most useful test to help establish a diagnosis is spirometry.

A classic pattern of airflow obstruction with a reduced forced expiratory volume in one second ( $FEV_1$ ) and reduced ratio of  $FEV_1$  to forced vital

capacity (FVC) is seen. Currently a diagnosis of airflow obstruction is based on the presence of a  $FEV_1/FVC$  ratio  $<0.7$  after bronchodilation.

However, there is increasing interest in using the 'lower limit of normal (LLN)' for the diagnosis of airflow obstruction. This would reduce incorrect diagnosis of COPD in older people, particularly men, who develop airflow obstruction due to aging-related loss of lung elastic recoil. This change may be introduced as part of the revised NICE/BTS/SIGN guideline and can be calculated automatically by most modern spirometers.

Classification of disease severity is usually based on spirometry results, but it is important to recognise that values obtained during spirometry can be poor predictors of functional limitation.

The main diagnostic conundrum remains in differentiating COPD from asthma. Factors more likely to be helpful are variable pattern of disease, a past history of asthma, atopy and smoking history. Normal spirometry will exclude COPD but unfortunately reversibility testing and steroid trials rarely confirm a diagnosis of asthma unless there is a dramatic improvement. It is important to emphasise that, even in specialist centres

	Symptoms and signs	Investigations
<i>COPD</i>	exertional breathlessness cough with sputum wheeze may be present overinflated chest	spirometry always abnormal
<i>Asthma</i>	variable symptoms including nocturnal dry cough and wheeze	spirometry may be normal peak flow variation large reversibility likely
<i>Bronchiectasis</i>	large volumes of purulent sputum recurrent lower respiratory tract infections	spirometry may be abnormal chest X-ray may be abnormal high-resolution CT scan shows bronchiectasis
<i>Chronic heart failure</i>	positional and exertional breathlessness elevated JVP and peripheral oedema tachycardia and crackles	ECG or chest X-ray abnormal

**Table 1.** Differential diagnosis of COPD

with a wide range of tests available, it can at times be very difficult to differentiate COPD from chronic asthma in a smoker (where there exists a fixed airflow obstruction pattern on spirometry).

The other main diagnoses to consider are heart failure and bronchiectasis. Although COPD and heart failure can co-exist, heart failure can usually be excluded on the basis of history and examination with ECG and chest X-ray results. Bronchiectasis and chronic bronchitis have overlapping symptoms, although production of large volumes of sputum (in excess of half a cupful per day) is usually associated with bronchiectasis. A comparison of the main differential diagnoses is shown in Table 1.

### Overall management

One of the most important aspects of COPD management is a positive attitude and encouragement of the individual concerned. Education and positive – but realistic – expectations should be emphasised.

Smoking cessation for those who continue to smoke and who wish to quit is the most important first step, but should never become a barrier to the availability of other treatments (with the exception of thoracic surgical interventions). Increasingly COPD patients are engaged in self-management, which can potentially lead to important benefits.

Under current recommendations from the England and Wales Home Oxygen Service cigarette smoking is not a contraindication to provision of home oxygen, but patients must be made aware of the dangers of smoking in the presence of oxygen and every effort should be made to encourage smoking cessation.

The role of diet should be emphasised as obesity may contribute to exertional breathlessness while reduced body mass index (BMI) is associated with a worse prognosis. Exercise in the form of pulmonary rehabilitation should be recommended, as it is more effective than many pharmacological interventions. Also important are annual influenza vaccinations and one-off pneumococcal vaccination.

The choice of drug treatment depends on disease severity and symptom profile. In mild disease, a short-acting bronchodilator for symptom control may be all that is needed. As disease severity – and particularly breathlessness – increases, then use of regular short- or long-acting inhaled or oral bronchodilators is appropriate. Patients with more severe disease and regular exacerbations will require additional treatment with inhaled corticosteroids, and here combination inhalers have a role. The most severely affected patients may need long-term domiciliary oxygen therapy, while surgery is only an option in a select group of individuals.

A broad approach to management is shown in Figure 1, and each of these interventions will be discussed in turn.

### Smoking cessation

The importance of smoking cessation should not be underestimated, regardless of disease severity, as quitting reduces both long-term mortality<sup>3</sup> and subsequent decline in lung function.<sup>4</sup> Self-reported cessation has also been shown to reduce hospitalisation later in life. Smoking cessation has dramatically changed over the last five years with most primary and secondary centres have access to specialist smoking cessation services. Although the days of advice from a doctor being the only support available have now passed, that advice is still an important component of treatment. Counselling and support groups should ideally be available and quit rates are improved when a cessation ‘contract’ is entered into and a specific ‘quit date’ chosen.

Adjuncts to cessation, which have been shown to improve quit rates in smokers, include nicotine replacement, bupropion (Zyban), nortriptyline (unlicensed use) and varenicline (Champix). Details of these therapies, their rate of efficacy and common side-effects are shown in Table 2. All have produced short-term quit rates in excess of 20 per cent and at times in

excess of 30 per cent, but realistically long-term rates of cessation are nearer 10-20 per cent. Reduction in the number of cigarettes smoked produces only financial benefits as similar nicotine and tar levels are usually obtained from a smaller number of cigarettes.

### Pulmonary rehabilitation

A formal exercise programme for patients with COPD has been shown to produce improvements in exercise capacity, activity level and health status.<sup>5</sup> This occurs at all levels of disease severity and the benefits obtained last for at least a year. It is recognised that exercise is important as part of a general 'healthy lifestyle' and continuation of exercise after a rehabilitation programme is encouraged.

Outpatient programmes are the norm in the UK and usually last six to eight weeks. Inpatient rehabilitation produces better results, but has not been taken up for a variety of reasons. Initial trials of rehabilitation immediately postexacerbation have shown excellent results and are being subjected to further analysis in larger studies. The exercise component is probably the most important part of the course and two supervised sessions per week with another unsupervised session at home is the usual format. The form of exercise does not appear to matter, although endurance training is most often used, while the education component provides an opportunity to promote patient empowerment.

As yet the use of nutritional supplementation, creatine and anabolic steroids to supplement exercise has produced disappointing results. Attempts to sustain the benefits of rehabilitation through maintenance programmes have also proved disappointing, and the reasons behind subsequent decline in function after one year are as yet unclear. Some programmes offer a repeat course after a period of time and there is evidence that this can be beneficial.

### Vaccination

All patients with COPD should be offered influenza vaccination on an annual basis and vaccination has been shown to reduce exacerbation rate and possibly mortality. Current guidelines recommend pneumococcal vaccination should also be given to all patients, but on one occasion only.

### Short-acting inhaled bronchodilators

Short-acting beta-agonists – salbutamol and terbutaline (Bricanyl) – are still a mainstay of treatment, although long-acting bronchodilators have been shown to be superior and are now prescribed at an earlier stage. The action of these drugs is by a decrease

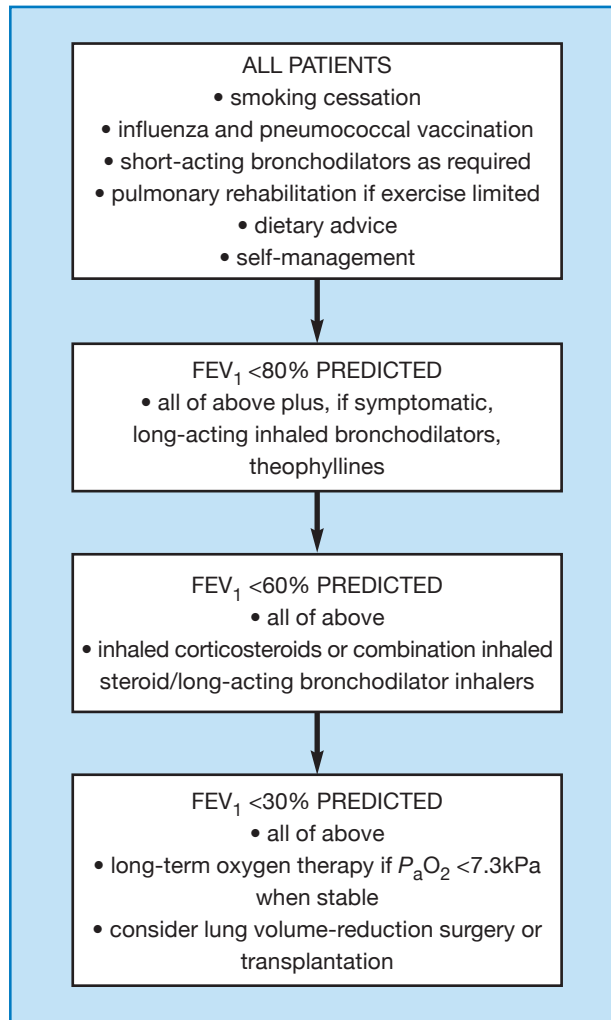


Figure 1. Overview of COPD management

in airway resistance and in the degree of dynamic hyperinflation during exercise. This latter change is not predicted by the results of reversibility testing. The aim in using these drugs is to produce symptom relief as their impact on more complex outcomes, such as quality of life, is disappointing.

### Long-acting bronchodilators

The aim in using long-acting bronchodilators is both to produce symptom relief, improve quality of life and reduce exacerbations. In terms of both consistency of bronchodilation and improvement in outcome measures long-acting beta-agonists – salmeterol (Serevent)<sup>6</sup> and formoterol<sup>7</sup> – and the long-acting anticholinergic tiotropium (Spiriva) are superior to their short-acting relatives.<sup>8</sup> Once-daily tiotropium is at least equivalent to, if not better than, twice-daily long-acting beta-agonists but a combination of the two is better still, as evidenced during a recent four-

Drug name	Form	Mode of action	Average 1-year quit rate achieved in trials	Main side-effects
<i>Nicotine replacement therapy</i>	chewing gum, transdermal patch, inhalator, nasal spray, sublingual tablet/lozenge	replaces nicotine obtained from cigarettes	17% with NRT vs 10% with placebo	local irritation at site of administration of nicotine
<i>Bupropion</i>	tablet	aminoketone antidepressant	19% with bupropion vs 10% with placebo	disturbed sleep, dry mouth, nausea and seizures – do not use in patients with current or past seizures
<i>Nortriptyline (unlicensed)</i>	tablet	tricyclic antidepressant	20% with nortriptyline vs 10% with placebo	dry mouth, drowsiness, light-headedness and constipation
<i>Varenicline</i>	tablet	nicotine receptor partial agonist	22% with varenicline vs 9% with placebo	nausea, sleep disturbance and headache

**Table 2.** Current smoking cessation drug options and their properties

year study.<sup>9</sup> This study also supported use of tiotropium at an earlier stage of disease (FEV<sub>1</sub> <70 per cent predicted). The efficacy of ‘ultra long-acting’ (once-daily) beta-agonists, such as indacaterol (not currently available), is being assessed in medium-term clinical trials.

The action of theophyllines, nonselective phosphodiesterase (PDE) inhibitors, is complex and they are unlikely to act purely as a bronchodilator. They do still have an add-on role in management but their relatively poor side-effect profile has relegated them to third-line therapy. Recent publications examining the efficacy of the selective PDE4 inhibitor roflumilast (not currently available)<sup>10</sup> have shown modest benefit to COPD patients with or without chronic bronchitis, but the impact in patients already taking inhaled corticosteroids is, as yet, unclear.

**Inhaled corticosteroids**

Inhaled corticosteroids (ICS) are the mainstay of asthma treatment but significantly less beneficial in COPD. However, it is clear that they produce modest, but significant, benefit. Large studies have shown that ICS do not arrest decline in lung function and have little role in early disease. Despite this, there is good evidence that they should be prescribed to patients with at least moderate airflow obstruction and, in particular, regular exacerbations as they decrease exacerbation rate, a finding confirmed in studies with

combination long-acting beta-agonist/inhaled corticosteroid inhalers (Seretide and Symbicort).

A three-year study of patients with a FEV<sub>1</sub> <60 per cent predicted has confirmed the long-term benefit of combination inhalers on lung function, exacerbation rate and health status, but it did not demonstrate a reduction in mortality.<sup>11</sup> This study also showed a small but significant increase in nonfatal pneumonia in patients taking high-dose inhaled steroids – a finding confirmed in a later, smaller study. Despite the benefits from taking ICS shown by these studies the physician should be alert to the development of pneumonia and patients advised accordingly.

No evidence exists that any one ICS is superior to any other, but at least moderate doses should be prescribed – 800µg per day of beclometasone dipropionate or budesonide<sup>7</sup> and at least 500µg per day of fluticasone.<sup>6,8</sup> However, there is no role for regular low-dose ‘maintenance’ oral steroids as they have been associated with muscle wasting and increased mortality.

**Drug delivery**

There are now a large number of devices available to deliver inhaled medication and choice of inhaler type is an important consideration when a prescribing decision is made. It is imperative that the patient is instructed on how to use a particular inhaler and that he or she is able to use it. Hence, assessment of inhaler technique is a vital part of COPD management.

Devices, including spacers, requiring a high flow rate for activation may be inappropriate for some individuals.

Evidence shows that inhaler preference varies between individuals and with age, and in an ideal sit-

uation a patient would be able to try a variety of inhalers and select the one that suits them best.

In formal trials looking at change in measures of airflow, there is little evidence to suggest that there is any difference between equal doses of drugs delivered by nebuliser or by metered-dose inhaler plus spacer. Despite this, a number of individuals achieve greater subjective benefit from drugs delivered by a nebuliser. It is difficult to make any specific recommendations for the long-term prescription of nebulised drugs, especially when considering both the expense and lifestyle restrictions involved. Therefore, requests should be considered on a case-by-case basis.

Classification	Mode of action	Main side-effects
<i>Anticholinergics, eg</i> short acting – ipratropium, oxitropium long acting – tiotropium	inhibit parasympathetic/vagal supply leading to bronchodilation	dry mouth occasional urinary retention
<i>Beta<sub>2</sub>-agonists, eg</i> short acting – salbutamol, terbutaline long acting – salmeterol, formoterol	sympathomimetic bronchodilators with relative specificity for the beta <sub>2</sub> -receptor; possibly some anti-inflammatory action	fine tremor tachycardia and palpitations headache anxiety/nervousness
<i>Mucolytics, eg</i> carbocisteine, erdosteine	antioxidants reversing glutathione depletion reduce sputum viscosity reduce bacterial adherence	bronchospasm, nausea, diarrhoea, rash
<i>Xanthines, eg</i> theophylline, modified-release theophylline, aminophylline, modified-release aminophylline	phosphodiesterase inhibition, adenosine antagonism; bronchodilator and anti-inflammatory actions	tachycardia and palpitations cardiac arrhythmias nausea and gastrointestinal upset insomnia headache
<i>Inhaled corticosteroids, eg</i> beclometasone, budesonide, fluticasone	topical anti-inflammatory agents, preventing production of cytokines and inhibiting cell activation	hoarseness oropharyngeal candidosis mild adrenal suppression with prolonged high doses increased risk of nonfatal pneumonia
<i>Oral corticosteroids, eg</i> prednisolone	systemic anti-inflammatory activity reducing cytokine production and cell activation	hypertension weight gain glucose intolerance osteoporosis and vertebral fractures

**Table 3.** Drugs used in the treatment of COPD, their modes of action and side-effects

**Mucolytics**

Mucolytic agents, such as carbocisteine (Mucodyne) and erdosteine (Erdotin), are frequently prescribed in COPD, particularly to patients who produce regular phlegm and have frequent exacerbations. Their likely mode of action is primarily as an antioxidant. They do not reduce long-term decline in lung function but reduce exacerbation rate in patients not already taking ICS.<sup>12</sup> However, it is unclear whether they are beneficial to patients already taking ICS.

**Home oxygen therapy**

Provision of domiciliary oxygen places a huge financial burden on the UK health services and the majority of these prescriptions are for people with COPD. Long-term oxygen therapy (LTOT) has a clearly defined role in that it lengthens survival in patients who have a resting arterial oxygen partial pressure ( $P_aO_2$ ) of less than 7.3kPa, measured when the individual is clinically stable.<sup>13</sup> For this benefit to be obtained, oxygen must be taken for at least 15 hours per day.

The individual may or may not feel any subjective benefit from therapy and, because of lifestyle restrictions inherent in this treatment, it is important that the goals of therapy are clearly explained to the individual concerned. Although taking oxygen for longer than 15 hours per day may produce additional mortality benefit, this has to be weighed against potential detrimental effects on quality of life from ‘tying’ patients to oxygen. Delivery of oxygen is usually from a concentrator via nasal speculae.

The prescription of home oxygen cylinders for use at the time of episodes of breathlessness – so-called ‘short-burst’ oxygen therapy – has little evidence base. However, prescription of oxygen in this form as part of palliative care delivery is appropriate. There is better evidence for use of oxygen during exercise as it improves endurance, though this form of oxygen is still infrequently prescribed in the UK.

Under 2006 UK national recommendations ambulatory oxygen should be provided to patients on LTOT plus active patients who shown evidence of oxygen desaturation on exercise with improvement of exercise capacity and/or breathlessness after provision of oxygen.

Organisation of oxygen services has improved over the last few years with a focus on rational prescribing.<sup>14</sup> How home oxygen services are organised will vary from area to area but any service will need to include LTOT assessment, ambulatory assessment and regular follow-up of patients prescribed home oxygen and will ideally include the capacity for assessment within the home.

The British Thoracic Society has considered the role of oxygen therapy during air flight, the guideline for which is currently being updated.<sup>15</sup> The current guideline recommends that individuals with resting oxygen saturations of below 92 per cent should breathe oxygen when flying. Individuals with saturations above 95 per cent do not need oxygen and those between these levels should be considered for a hypoxic challenge test, which some centres can now provide.

Airlines have very different policies for the provision of oxygen to passengers, ranging from free provision to a large additional fee. Provision of in-flight oxygen should be arranged in good time beforehand and patients taking LTOT will need to ensure that similar arrangements are in place at their destination.

### Noninvasive ventilation

There is now a clear role established for use of nasal ventilation in the setting of an acute exacerbation. The role of this therapy in the chronic situation is less clear and, although there may be quality-of-life benefits for some carefully selected individuals, there are as yet no convincing data showing an improvement in life expectancy. Currently, this form of treatment is not routinely used as part of chronic management but is being examined in large multicentre trials.

### Surgery

Resection of large emphysematous bullae in certain individuals can lead to significant objective benefits. The role of lung volume-reduction surgery – resection of damaged areas of lung in the expectation that the remaining lung will function more efficiently and effectively thereafter – is now more clearly defined.<sup>16</sup>

Careful patient selection is imperative because relatively few are likely to benefit from this form of treatment. Individuals with very severe airflow obstruction (FEV<sub>1</sub> less than 20 per cent predicted) and either a very low level of oxygen diffusion or widespread ‘homogeneous’ emphysema have a very high mortal-

Indicator	Points
<i>Records</i> COPD 1. The practice can produce a register of patients with COPD	3
<i>Initial diagnosis</i> COPD 12. The percentage of all patients with COPD diagnosed after 1 April 2008 in whom the diagnosis has been confirmed by postbronchodilator spirometry	5
<i>Ongoing management</i> COPD 8. The percentage of patients with COPD who have had influenza immunisation in the preceding 1 September to 31 March COPD 10. The percentage of patients with COPD with a record of FEV <sub>1</sub> in the previous 15 months COPD 13. The percentage of patients with COPD who have had a review undertaken by a healthcare professional in the preceding 15 months, including an assessment of breathlessness using the MRC dyspnoea score	6 7 9

**Table 4.** Quality indicator points for COPD, 2009

ity with the procedure and should not be considered. Patients with severe emphysema along with predominant upper lobe disease and also marked exercise impairment are most likely to benefit.

Patient selection should be performed in secondary care but referral can be considered for patients who meet the above criteria, have an FEV<sub>1</sub> of less than 45 per cent predicted and who no longer smoke.

Newer techniques to produce lung volume reduction include placement of endobronchial valves, which can be inserted bronchoscopically. Case series have suggested that the technique is relatively safe and can produce effective volume reduction leading to improved outcomes. However, it is as yet unclear which patients should be offered treatment and when they should be offered it.

Single-lung transplantation is performed for emphysema but numbers are small – in part a reflection of the shortage of donor organs. The procedure usually leads to excellent functional and quality-of-life benefits but there is an absence of survival benefit – survival being equivalent to those individuals remaining on the transplant list. Although there is usually no

'formal' age limit, the chances of transplantation reduce with age, often due to co-morbidity.

### Treatment of exacerbations

Exacerbations are a common occurrence in COPD, although their frequency varies dramatically from individual to individual. They become more common as lung function worsens, and patients who suffer more frequent exacerbations report lower quality-of-life scores. Hence, reduction in exacerbation rate is an important treatment goal in COPD, particularly as the 2008 National COPD audit showed that 13.9 per cent of patients die within 90 days of hospitalisation due to an exacerbation of COPD.

Timely treatment of exacerbations is important, with both viral and bacterial infections accounting for a third or more of exacerbations. Hence, antibiotic therapy for the exacerbation is recommended when there is an increase in breathlessness associated with either a change in sputum colour or an increase in sputum volume.

There are many local antibiotic policies that incorporate local patterns of resistance but, in general, appropriate treatment for acute bronchitis would be an aminopenicillin (or macrolide if penicillin aller-

- guidelines help to optimise patient management
- accurate diagnosis is essential
- pulmonary rehabilitation helps patients with functional limitation at all disease stages
- inhaler technique should be assessed in all patients to optimise drug delivery
- long-acting bronchodilators produce the best patient outcomes
- inhaled steroids are useful in patients with moderate to severe disease who have 3 exacerbations in 2 years
- suitability for long-term oxygen therapy should be formally assessed

**Table 5.** Summary of key points

gic). There now exists limited evidence suggesting medium-term benefit in some patients from prescription of long-term erythromycin, with the impact probably due to its anti-inflammatory rather than anti-infective properties.

There is now a strong evidence base advocating the use of short-course oral steroids at the time of an acute exacerbation.<sup>17</sup> The main benefit is an improvement in the speed of recovery. An appropriate treatment is a seven-day course of 30mg oral

prednisolone, which can be stopped abruptly. Increasing bronchodilator dose at the time of an exacerbation is also logical.

It is now firmly established that up to 25 per cent of patients previously admitted to hospital with a COPD exacerbation can be safely cared for at home through a 'hospital at home' service. Various service models exist based around admission prevention, early supported discharge or a combination. No particular model is superior, allowing the development of a service according to local factors. The BTS has published a newly developed 'hospital at home' guideline.<sup>18</sup>

The evidence that COPD integrated care leads to a reduction in hospital admissions is conflicting but there is UK evidence suggesting a benefit.<sup>19</sup> It may be that the effectiveness of 'case management' will vary according to the model of healthcare provision in a particular region or country.

### Conclusion

There is an increasingly strong evidence base for many interventions used in the treatment of COPD. A summary of major points is shown in Table 5. No longer is a nihilistic approach appropriate, but the goals of each treatment should be recognised and, in this way, treatment can become patient centred.

Management of the disease requires a true multi-disciplinary approach, and different individuals are likely to benefit from intervention from both hospital and family doctors and nurses, physiotherapists, occupational therapists, dietitians and counsellors. Most encouragingly, implementation of therapies with a strong evidence base can bring benefits to patients with this chronic debilitating condition.

## Resources

### Groups and organisations

British Lung Foundation. Tel: 020 7688 5555; helpline: 08458 505020 (Mon-Fri 10am-6pm); website: [www.lunguk.org](http://www.lunguk.org).

British Thoracic Society. Tel: 020 7831 8778; e-mail: [bts@brit-thoracic.org.uk](mailto:bts@brit-thoracic.org.uk); website: [www.brit-thoracic.org.uk](http://www.brit-thoracic.org.uk).

Chest, Heart & Stroke Scotland. Tel: 0131 225 6963; e-mail: [admin@chss.org.uk](mailto:admin@chss.org.uk); website: [www.chss.org.uk](http://www.chss.org.uk).

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[www.cks.nhs.uk/chronic\\_obstructive\\_pulmonary\\_disease](http://www.cks.nhs.uk/chronic_obstructive_pulmonary_disease).

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### Patient information

Patient UK ([www.patient.co.uk](http://www.patient.co.uk)) provides information leaflets and patient factsheets on COPD, inhalers for COPD, controlled breathing, smoking – the facts, use of oxygen therapy in COPD, acute exacerbations of COPD, breathlessness, spirometry and others.