

## Treatment

The treatment of COPD includes drug therapy, surgery, exercise and counselling/psychological support. When managing COPD patients, it is particularly important to evaluate the social and family circumstances, and not to treat the patient in isolation. Interventions at home, such as the installation of a stair lift, may have a considerably greater impact on a patient's quality of life than adding another drug therapy.

Management of symptomatic patients centres around the relief of symptoms, optimization of lung function, improvement in activities, prevention of exacerbations and prevention of complications. The holy grail of COPD management is to prevent or reduce disease progression, but at present the only treatment known to achieve this is long-term oxygen therapy in chronically hypoxic patients.

### Guidelines

Guidelines on the management of COPD were published by the BTS in 1997.<sup>2</sup> North American guidelines on the management of COPD<sup>7</sup> and a European Consensus Statement<sup>8</sup> were published in 1995. These are all under revision, but the latest COPD guidelines come from the Global Initiative for Chronic Obstructive Lung Disease (GOLD).<sup>9</sup> This initiative was established by the US National Heart, Lung & Blood Institute (NHLBI) in conjunction with the World Health Organization (WHO). Its goals are "to increase awareness of COPD and decrease mortality and morbidity" from COPD by encouraging research and making consensus-based recommendations on management of COPD.

### Assessing the outcome of interventions

Traditionally, the effects of interventions have been assessed by measuring changes in the FEV<sub>1</sub> but, by definition, there is

### Outcome measures

Spirometry  
Walking distance  
Dyspnoea indices  
Symptom scores  
Health status  
Exacerbation rate

**Table 26.** Outcome measures.

limited scope for this to change and other outcome measures must be considered (Table 26). Other spirometric indices such as the slow vital capacity (SVC) and inspiratory capacity (IC) may correlate better with the clinical response to therapy;<sup>102</sup> improvements in patient-centred outcomes such as symptoms, exercise capacity and health status may occur without significant changes in FEV<sub>1</sub><sup>103</sup> and reductions in the frequency of exacerbations may also be relevant. Studies showing differences in these alternative outcome measures must be sufficiently powered to allow interpretation.

### Smoking cessation

Smoking cessation advice and therapy remain crucial in all patients with COPD, whatever the severity.<sup>104,105</sup> Stopping smoking returns the accelerated rate of decline in FEV<sub>1</sub> seen in smokers (Figure 4) back to the normal rate.<sup>12,106</sup> Basic anti-smoking advice should be given to all smokers as part of an integrated service offering counselling and support.<sup>107</sup> Recent advances in the pharmacotherapy of nicotine addiction have led to significantly higher quit rates<sup>108</sup> and bupropion has been shown to be effective in patients with COPD.<sup>99</sup> Demonstrating to patients that their lungs have already been damaged by smoking by performing spirometry also appears to improve quit rates.<sup>109</sup>

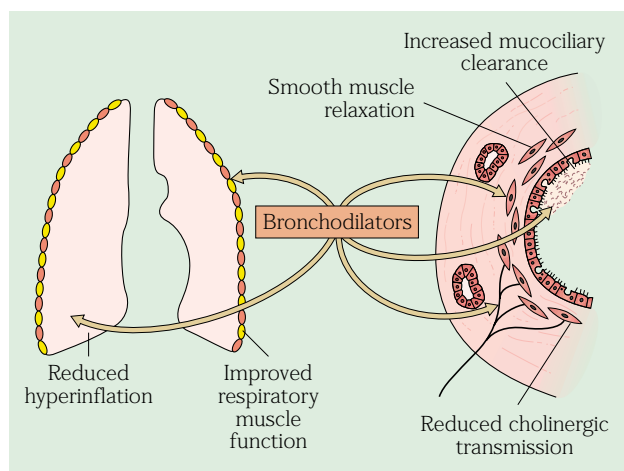
## Drug therapy in stable disease

### Bronchodilators

Although the disease is characterized by substantially irreversible airflow obstruction, bronchodilators are still the mainstay of pharmacotherapy.<sup>2,9</sup> Beta agonists, anticholinergics and theophylline are all effective bronchodilators in COPD. The choice of therapy depends on individual responses.

The structural changes in the airways prevent bronchodilators returning airway calibre to normal, and clinically relevant improvements in FEV<sub>1</sub> may be too small to identify against the background day-to-day variation. Inhaled agents are preferred to oral because of the reduction in systemic side-effects. Beta agonists act directly on bronchial smooth muscle to cause bronchodilation, whereas anticholinergics act by inhibiting resting broncho-motor tone. Both classes of drugs act synergistically to reduce airway resistance and reduce hyperinflation (Figure 27).

As discussed above, single dose bronchodilator reversibility tests are important in the assessment of patients with COPD;



**Figure 27.** Diagram showing the effects of bronchodilators on airways and respiratory mechanics in patients with COPD.

however, they do not predict the symptomatic benefit that patients may obtain from bronchodilator therapy.<sup>110</sup> Bronchodilators may increase FEV<sub>1</sub>, FVC or exercise tolerance independently, but an increase in FEV<sub>1</sub> does not correlate well with an improvement in symptoms. As well as increasing airway calibre, these drugs lead to a reduction in pulmonary hyperinflation, increase mucociliary clearance and improve respiratory muscle function.<sup>111</sup> All of these actions may contribute to the clinical benefit, but most trials have only used changes in FEV<sub>1</sub> as the outcome measure.

**Short-acting beta agonists** Beta agonists are the most widely used bronchodilators for COPD. The dose–response relationship for salbutamol in patients with largely or completely irreversible COPD is almost flat.<sup>112,113</sup> The time to peak response is slower than in asthmatics and the side-effect to benefits ratio is such that there is little benefit in giving more than 1 mg salbutamol. They are effective for up to 4 hours and can be used both on a regular or an as required basis.

Patients who do not have a significant spirometric response may still benefit if alternative outcome measures such as walking distances are assessed. Studies comparing short-acting beta agonist with placebo have shown significant increases in FEV<sub>1</sub>, PEF and symptom scores (Table 27).<sup>114</sup> Beta agonists do not have any significant effect on cough or sputum production, and their effects on walking distance have been inconsistent.

**Long-acting beta agonists** The physiological effects of long-acting beta agonists are similar to the short-acting agents, but

### Effects of short-acting beta agonists

- Increased FEV<sub>1</sub>
- Reduced breathlessness
- Increased exercise capacity
- Improved health status

**Table 27.** Effects of short-acting beta agonists.

their duration of action is around 12 hours. Salmeterol has a slower onset of action than eformoterol.

Some patients with COPD undoubtedly get symptomatic benefit. Studies have shown that they produce improvements of approximately 1–200 ml in FEV<sub>1</sub> and they improve health status and breathlessness scores (Table 28).<sup>115–119</sup> These effects are dose dependent and maximum improvement in health status is produced by salmeterol (50 µg) or eformoterol (12 µg) twice daily.<sup>118,119</sup> Larger doses have a reduced effect.

Long-acting beta agonists appear to reduce exacerbation rates in COPD, but the mechanism responsible for this remains unclear. Effects on host defences have been proposed,<sup>120</sup> but it is possible that the effects are due to a reduction in baseline breathlessness, which leads to reduced recognition of exacerbations as a result of increased tolerance of the increased breathlessness that occurs.

Long-acting beta agonists are more expensive than short-acting drugs, but in patients who respond they are more convenient.

**Anticholinergics** Cholinergic nerves are the main neural bronchoconstrictor pathway in the airways and the resting tone is increased in patients with COPD.<sup>121</sup> Cholinergic effects on the airway are mediated by muscarinic receptors and these also mediate effects on mucus secretion. Three muscarinic receptors are now recognized: M<sub>1</sub> receptors mediate cholinergic transmission in parasympathetic ganglia, M<sub>2</sub> receptors mediate feedback inhibition of acetylcholine (ACh) release from

### Effects of long-acting beta agonists

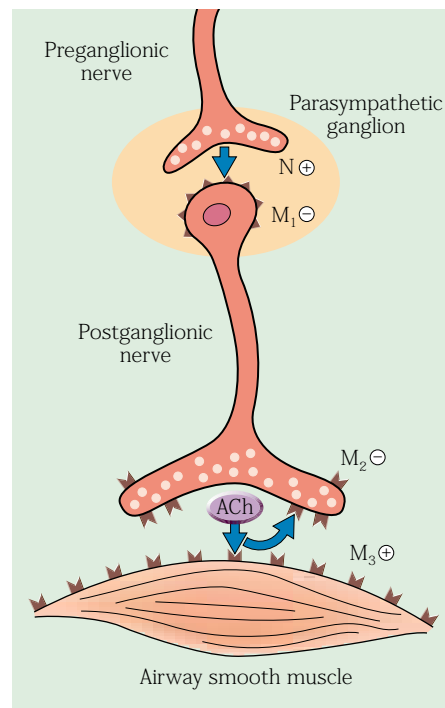
- Improved FEV<sub>1</sub>
- Reduced symptoms
- Increased exercise tolerance
- Improved health status
- Reduced exacerbation rate

**Table 28.** Effects of long-acting beta agonists.

preganglionic nerves and M<sub>3</sub> receptors mediate smooth muscle contraction (Figure 28). Effective anticholinergic drugs block M<sub>1</sub> and M<sub>3</sub> receptors in preference to M<sub>2</sub> receptors, as inhibition of these facilitates ACh release.<sup>122</sup>

The speed of onset of action of ipratropium and oxitropium is slower than short-acting beta agonists, but they produce more sustained bronchodilatation (up to 8 hours) and are at least as effective, and possibly more so.<sup>124–126</sup> Unlike the beta agonists, anticholinergic bronchodilators have also been shown to have a beneficial effect on sleep quality in patients with COPD.<sup>127</sup> The optimal dose of ipratropium is around 80 µg, which is higher than the dose usually prescribed.<sup>128</sup>

A long-acting anticholinergic bronchodilator (tiotropium bromide) which can be given once daily<sup>129</sup> and which has kinetic



**Figure 28.** The roles of muscarinic cholinergic receptors in the airways. Reproduced with permission from Barnes PJ. Modulation of neurotransmission in airways. *Physiol Rev* 1992; **72**(3): 699–729.<sup>123</sup>

selectivity for  $M_1$  and  $M_3$  receptors<sup>130</sup> has recently been developed. This appears to be an effective bronchodilator which reduces breathlessness, improves exercise tolerance, reduces exacerbations and improves health status.<sup>129,131,132</sup>

Anticholinergic bronchodilators should be tried in patients who remain symptomatic despite using short-acting beta agonists. They may be used as combination therapy (see below) or alone, but current guidelines suggest that combination therapy is best reserved for patients who fail to get adequate symptom relief from single agent therapy (Table 29).

**Combination therapy** Giving short-acting beta agonists at the same time as anticholinergic bronchodilators leads to greater increases in  $FEV_1$ , or other measures of airway calibre, than either alone.<sup>133–136</sup> Combination therapy may produce greater symptom relief with fewer side-effects than increasing the dose of a single agent, but may be more expensive. Inhalers containing combinations of ipratropium and salbutamol are also available and offer greater convenience.<sup>126</sup>

**Methylxanthines** The mechanism of action of methylxanthines remains uncertain.<sup>137</sup> Their primary effect is generally assumed to be relaxation of airway smooth muscle; however, at therapeutic concentrations they have little direct bronchodilator effect. Theophyllines are used in COPD but their use is declining.<sup>138</sup>

Sustained release, oral theophylline and aminophylline produce symptomatic relief and improvements in  $FEV_1$ .<sup>139,140</sup>

### Effects of anticholinergics

- Improved  $FEV_1$
- Reduced symptoms
- Increased exercise tolerance
- Reduced exacerbations
- Improved health status
- Improved sleep quality

**Table 29.** Effects of anticholinergics.

They appear to be less effective than long-acting beta agonists<sup>141</sup> and as such are now usually reserved as third-line therapy, usually in combination with inhaled therapy.<sup>142</sup>

Because of potential toxicity and significant interactions with other drugs,<sup>143</sup> they require monitoring of plasma concentrations.<sup>144</sup> The therapeutic index of theophylline is narrow and some patients experience significant side-effects, even when the plasma levels are in the therapeutic range. Ageing-associated changes in liver function lead to a greater risk of toxicity in the elderly.<sup>145</sup> For most patients a measurement of plasma theophylline concentrations 8–10 hours following a single oral dose will be sufficient to predict maintenance requirements and a repeat measurement 1–2 weeks later will confirm that the plasma concentration is in the therapeutic range. 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 (Table 30).

### Corticosteroids

Although inflammatory changes are present in the airways of patients with COPD, the role of corticosteroids remains controversial.

**Oral steroids** At best, trials of oral corticosteroids in patients with stable disease have shown improvements in small subsets (15–40%);<sup>146</sup> however, this may be achieved at considerable cost in terms of side-effects and at present there is no means

### Theophylline

- Used third-line when fail to respond to inhaled beta agonists and anticholinergics
- Side-effects (nausea and tachycardia) may be problematic
- Plasma concentrations need monitoring
- Plasma levels affected by concomitant therapy and smoking

**Table 30.** Theophylline.

of predicting those who will respond. Less than half of those patients who show objective improvements with oral therapy maintain the improvement on inhaled corticosteroid therapy.<sup>147</sup>

Trials of oral steroid therapy can help to identify patients with significant untreated chronic asthmatic component to their disease,<sup>148</sup> who may benefit from being managed according to asthma protocols, but they are poor predictors of response to inhaled steroids in patients with COPD.<sup>149</sup> Nevertheless, current guidelines recommend that patients showing a good response to oral corticosteroids should be treated along similar lines to asthmatics.<sup>2</sup>

Uncontrolled retrospective studies have suggested that oral corticosteroid therapy can slow the decline in FEV<sub>1</sub>, but there is insufficient evidence to recommend this.

The role of oral steroids (Table 31) in the management of acute exacerbations is discussed later (p. 74).

Oral steroids carry with them a dose- and duration-dependent risk of systemic side-effects.<sup>150</sup> There is some individual variability in the susceptibility to the development of side-effects. Patients may notice increased appetite, fluid retention and mood swings with short-term treatment. With longer term, high dose treatment patients may develop skin thinning, easy bruising, weight gain, osteoporosis, cataracts, proximal myopathy, diabetes and hypertension. Patients should be made aware of these effects and when appropriate they should be prescribed therapy (such as hormone or bisphosphonate therapy) to reduce the risk of osteoporosis.

### Role of oral steroids

- Identification of patients with significant asthmatic component
- Speed recovery from an exacerbation
- Delay time to next exacerbation
- Produce sustained reduction in symptoms in a very small proportion of patients
- Significant risk of side-effects

**Table 31.** Role of oral steroids.

**Inhaled steroids** The role of inhaled steroids in stable COPD is controversial and has been the subject of four recent large trials.<sup>151–154</sup> All used changes in the rate of decline in FEV<sub>1</sub> as the primary end-point and showed no benefit. Inhaled steroids appear to reduce the number of exacerbations in patients with severe COPD<sup>153–155</sup> and this may be the main benefit of treatment (Table 32). High dose inhaled steroids in patients with COPD may reduce bone mineral density<sup>154</sup> and the benefits must be balanced against such side-effects.<sup>150</sup> Inhaled steroids should be reserved for patients with severe COPD (FEV<sub>1</sub> <40% predicted) who are having frequent exacerbations.

### Delivery systems

As with asthma, delivery of the drugs to the lungs is an essential part of pharmacotherapy. When considering delivery devices, co-existing problems, such as arthritis, must be taken into account. Pressurized metered dose inhalers (pMDIs) are cheap but unless used with large-volume spacers give poor pulmonary deposition, and as many as three-quarters of patients with COPD are unable to use them correctly.<sup>156</sup> Dry powder devices are more expensive but can be used successfully by up to 90% of patients and thus may be significantly more cost-effective. Many elderly patients soon forget how to use their inhalers correctly<sup>157</sup> and it is essential to check their inhaler technique at every opportunity and re-instruct as necessary.

### Role of inhaled steroids

- No effect on disease progression
- May reduce exacerbation rates in patients with severe disease
- May slow rate of decline in health status

**Table 32.** Role of inhaled steroids.

**Large-volume spacers** The use of large-volume spacers with metered dose inhalers is a well-established method of maximizing pulmonary drug deposition in patients with asthma, but there have been few studies in COPD. Poor co-ordination may significantly impair an elderly patient's ability to use a metered dose inhaler and this can be improved using a large-volume spacer (see Table 33).<sup>156</sup>

**Nebulizers** Most patients achieve maximum possible bronchodilatation with drugs administered by conventional inhalers, but a few derive benefit from very high doses of bronchodilators.<sup>158,159</sup> These high doses are most conveniently delivered using a nebulizer. Some patients may also derive benefits from the moistening or cooling effects of the aerosol generated by a nebulizer, but there is conflicting evidence about whether there is any advantage in delivering the same doses of drugs delivered by inhaler or nebulizer.<sup>160-164</sup>

Compressors to drive nebulizers are relatively cheap, but the drug costs are high and patients may experience more severe systemic effects. For a few patients, there does appear to be a

### Factors affecting choice of delivery systems

- Dexterity
- Hand grip strength
- Co-ordination
- Severity of airflow limitation

**Table 33.** Factors affecting choice of delivery systems.

### Indications for nebulized therapy

- Persistent symptoms despite adequate bronchodilators therapy from inhalers
- Inability to use inhalers
- Exacerbations

**Table 34.** Indications for nebulized therapy.

small advantage in using nebulized therapy, but these patients should have tried maximal doses of inhaled therapy, have had a trial of oral steroids and have a formal assessment of the efficacy of nebulized therapy.<sup>165</sup>

The BTS nebulizer guidelines make recommendations about the assessment of patients for nebulizer therapy.<sup>165</sup> As discussed earlier, patients may derive significant symptomatic benefit from nebulized therapy compared with inhaled therapy without having a significant change in FEV<sub>1</sub>. This limits the value of objective assessments of nebulizer therapy and the best assessment may simply be to ask the patients whether they are able to do more, or whether they have fewer symptoms as a result of using nebulized bronchodilators and whether or not they have experienced any adverse effects.

The role of nebulized therapy during exacerbations is discussed on p. 73. They are frequently used despite the fact that there is again conflicting evidence about the comparative efficacy of the same doses of drug given by nebulizer and inhaler. Nebulizers are often preferred because they are easier to administer<sup>166</sup> and because drug deposition is not dependent on inspiratory effort (Table 34).

### Indications for referral for a specialist opinion

Most patients with COPD can be managed in primary care but some may require referral to a specialist (Table 35). This may

### Indications for referral

- Diagnostic uncertainty
- Disproportionate symptoms
- Persistent symptoms
- Development of lung cancer
- Pulmonary rehabilitation
- Nebulizer assessment
- Oxygen assessment

**Table 35.** Indications for referral.