

The management of chronic obstructive pulmonary disease (COPD)

Summary

- All COPD patients who are still smoking should be offered help to stop at every opportunity.
- Long-acting bronchodilators are recommended where patients continue to have significant symptoms or deteriorate despite the use of short-acting bronchodilators, and for patients who have at least two exacerbations of COPD each year. No consistent difference in health outcomes has been found between long-acting β_2 -agonists (LABAs, e.g. salmeterol and formoterol) and tiotropium. Therefore, drug choice depends on individual factors and cost.
- Inhaled corticosteroids should be reserved for patients with moderate or severe COPD ($FEV_1 \leq 50\%$ predicted) and added to long-acting bronchodilators in certain circumstances (see text for details). Use of fixed combination inhalers should be considered on an individual basis.
- There is good evidence for the benefits of pulmonary rehabilitation, and it should be offered to all patients with COPD who consider themselves functionally disabled.



Introduction

Nearly 900,000 people in the UK are diagnosed as having chronic obstructive pulmonary disease (COPD), and half as many again are thought to be living with undiagnosed COPD.¹ The disease produces symptoms and disability that impair quality of life and lead to substantial morbidity and mortality.^{1,2} Up to one in eight hospital admissions may be due to COPD.¹ The true mortality rate is unclear but, in 2004, approximately 23,000 deaths in England and Wales were recorded as being due to COPD.^{1,3} It has been estimated that COPD costs the NHS around £982 million each year.¹

COPD is characterised by airflow obstruction, which is usually progressive, not fully reversible, and does not change markedly over several months.¹ The airflow obstruction is due to a combination of airway and parenchymal damage and is associated with chronic inflammation, which differs from that seen in asthma. COPD is usually caused by smoking.¹

In 2004, the National Institute for Health and Clinical Excellence (NICE) issued a guideline for COPD, which is endorsed by the British Thoracic Society.¹ The guideline offers best practice advice on the identification and care of patients with the disease.

This *Bulletin* considers selected aspects around the management of stable COPD that

have been recently updated, or are particularly relevant to primary care. It does not consider acute management or long-term oxygen therapy. A related *MeReC Briefing*, No. 33 May 2006 (www.npc.co.uk/merec.htm) provides a wider overview of diagnosis and management, including spirometry, reversibility testing, pulmonary rehabilitation and mucolytic therapy. For a comprehensive review of the diagnosis and management of COPD, please refer to the full NICE guideline (www.nice.org.uk). The General Practice Airways Group has also produced a useful guide on the diagnosis and management of COPD in primary care, which is based on the NICE guideline (see www.gpiag.org/news/copd_guide.php).

Management of stable COPD

The management of individual patients with COPD should be guided by their symptoms and level of disability. Effects of the disease occurring outside the lungs (e.g. weight loss, muscle weakness, anxiety and depression) should also be assessed. The **Figure** (Page 19) outlines the overall management strategy recommended by NICE.¹

Smoking cessation is the only intervention shown to reduce the rate of decline in lung function.⁴ Smoking cessation intervention programmes in people with asymptomatic airways obstruction can also reduce mortality.⁵ Therefore, all COPD patients who are still

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There is good evidence from RCTs that pulmonary rehabilitation improves breathlessness, exercise capacity and health-related quality of life

smoking, regardless of age, should be offered help to stop at every opportunity.¹ A full discussion of smoking cessation is outside the scope of this *Bulletin*, but *MeReC Briefing* No. 33 lists some further sources of information.

There is good evidence from randomised controlled trials (RCTs) for the benefits of **pulmonary rehabilitation**, which has been shown to improve breathlessness, exercise capacity and health-related quality of life.⁶ The benefits appear to be greater than those of bronchodilator drugs.⁶ There is also evidence from some RCTs that pulmonary rehabilitation is effective in reducing the need for hospitalisation in patients with severe airway obstruction.⁷ NICE recommends that pulmonary rehabilitation is offered to all people with COPD who consider themselves functionally disabled (usually Medical Research Council [MRC] grade 3 and above).¹ However, it is not suitable for people who are unable to walk, have unstable angina, or have had a recent myocardial infarction.¹

Drug treatments may relieve breathlessness, improve exercise tolerance, reduce exacerbations and improve quality of life, but patients still have an underlying reduced lung function.¹ In patients who remain symptomatic, the NICE guideline recommends stepping up drug therapy. However, it must be recognised that no drug used in COPD fully relieves symptoms. Treatment should be reviewed regularly, and polypharmacy minimised where possible. The clinical effectiveness of combined treatments can be assessed by improvements in symptoms, activities of daily living, exercise capacity and lung function. Therapy should be stopped if there is no benefit after four weeks.¹

Outcomes in COPD

An important improvement in the management of COPD has been a change in focus on the patient outcomes considered to be important. Previously, the effect of drug therapy on the rate of decline in FEV₁ was used to assess its value,⁸ whereas reducing exacerbations and breathlessness, and improving quality of life and exercise performance, are now considered more appropriate patient-oriented outcomes (POOs),⁹ i.e. does the patient live longer or have a better quality of life? Unfortunately, the lack of a standard definition of an exacerbation, in terms of frequency and severity, often precludes any accurate comparison between trials.

What is the role of long-acting bronchodilators?

A short-acting bronchodilator (β_2 -agonist e.g. salbutamol or terbutaline, or an anticholinergic i.e. ipratropium) 'as necessary' is recommended as the initial treatment of breathlessness and exercise limitation in COPD. If patients continue to have significant symptoms or deteriorate,

stepping-up to include either combined therapy with a short-acting β_2 -agonist and a short-acting anticholinergic, or therapy with a long-acting bronchodilator is recommended. Long-acting bronchodilators include long-acting β_2 -agonists (LABAs) e.g. **salmeterol** or **formoterol**, and the anticholinergic **tiotropium**[▼]. They are specifically recommended for patients who remain symptomatic on short-acting bronchodilators, and for those who have at least two exacerbations of COPD each year.¹

Tiotropium[▼] (*Spiriva*[®]) is structurally related to ipratropium bromide, but has a long duration of action, allowing it to be taken once daily.¹⁰ A Cochrane review of nine RCTs (n=6,584, up to 12 months) concluded that tiotropium reduced COPD exacerbations and related hospitalisations, and may reduce the decline in lung function, **compared with placebo or ipratropium**.¹¹ In the only RCT comparing it with ipratropium, tiotropium reduced the absolute risk of COPD exacerbations by about 11% (number needed to treat [NNT] nine over one year, odds ratio [OR] 0.64 95% CI 0.44–0.92). There was no significant difference between the two drugs in the proportion of patients hospitalised for COPD exacerbations. Tiotropium improved health related quality of life and symptom scores among patients with moderate and severe disease compared with both placebo and ipratropium.¹¹

Further RCTs are required to assess the effectiveness of tiotropium in mild and very severe COPD, and also to consider its effects on mortality and decline in lung function.¹¹ The dose of ipratropium in RCTs was 40mcg four times a day;¹¹ and RCTs with high doses of 80mcg four times a day, which are often used in clinical practice, are required.¹⁰

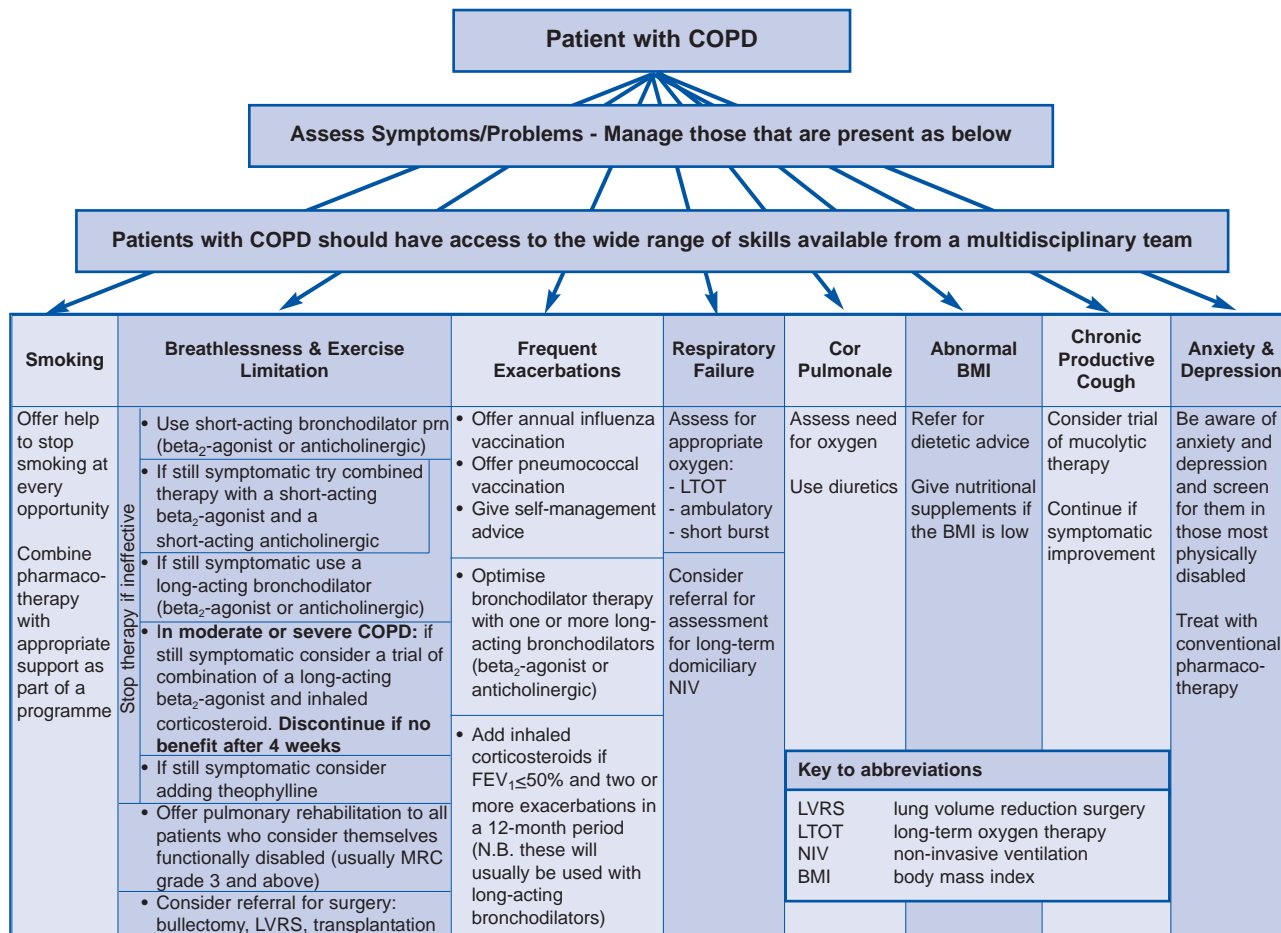
Dry mouth was the most common adverse effect of tiotropium (about 14% of patients) in one-year studies, but it was usually mild and often resolved as treatment continued.¹² More patients developed dry mouth with tiotropium than with ipratropium (12.1% vs. 6.1%, P<0.05) in comparative studies.¹³ Other common adverse effects of tiotropium (affecting 1–10% of patients) include constipation, candidiasis, sinusitis and pharyngitis.¹² Care should be taken to avoid co-prescription of preparations containing anticholinergics.

In a recent Canadian health technology assessment, 33 RCTs (up to one year's duration) of the **LABAs, salmeterol** and **formoterol**, in mild to severe COPD were systematically reviewed.¹⁴ LABAs reduced hospitalisations and exacerbations of COPD **compared with placebo**. However, no consistent improvements in health outcomes were seen when LABAs were **compared with ipratropium or tiotropium** in eight RCTs (n>3,500). More robust data was available for salmeterol than formoterol.¹⁴

No consistent improvements in health outcomes were seen when LABAs were compared with ipratropium or tiotropium

Figure: Management of stable COPD¹

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Palliative Care

Opiates can be used for the palliation of breathlessness in patients with end stage COPD unresponsive to other medical therapy. Use benzodiazepines, tricyclic antidepressants, major tranquilisers and oxygen when appropriate. Involve multidisciplinary palliative care teams.

Salmeterol seems less well tolerated than tiotropium. Based on two RCTs (n=807), more people withdrew because of adverse events with salmeterol than with tiotropium (OR 2.16, 95% CI 1.36–3.43). There were no data available to compare formoterol with tiotropium.¹⁴ The most common immediate adverse effect of β₂-agonists is tremor, which tends to be worse in the first few days of treatment.¹³

Further long-term studies (over several years) are required to evaluate the effects of both tiotropium and LABAs on mortality and change in FEV₁, and to clarify their roles in comparison to, or in combination with, one another. Drug choice should be influenced by the patient's preference, their response to a trial of the drug, side effects, cost and ease of use.

When should an inhaled corticosteroid be added to treatment?

NICE recommends that an inhaled corticosteroid (ICS) is added to a LABA where patients with an FEV₁ ≤ 50% of predicted (i.e. **moderate or severe COPD**) are still breathless despite monotherapy with a LABA or

tiotropium. They also make a more general recommendation of adding an ICS to a long-acting bronchodilator (a LABA or tiotropium) in patients with moderate or severe COPD, who are having two or more exacerbations requiring treatment with antibiotics or oral corticosteroids in a 12-month period. However, we are not aware of any evidence for combining tiotropium with an ICS in COPD. Clinicians should be aware of the potential risk of osteoporosis and other side effects in patients using a high-dose ICS (especially if they have other risk factors e.g. are postmenopausal). These risks should be discussed with patients. None of the inhalers containing an ICS alone are currently licensed for use in COPD, and the responsibility for such unlicensed use lies with the prescriber.¹

RCTs have shown that ICSs are unlikely to have any clinically significant effect on the **decline in FEV₁** in COPD patients in the long-term.^{8,15,16} The NICE recommendations around the use of ICSs in COPD aim to reduce **exacerbation rates** and slow the decline in health status (i.e. improve quality of life). This is based, at least partially, on secondary outcome data from several RCTs.^{1,17–19}

Inhaled corticosteroids are only recommended for certain patients with moderate or severe COPD (FEV₁ ≤ 50% predicted)

The use of fixed combination inhalers should be considered on an individual basis

A systematic review of nine RCTs (n=3,976, ≥6 months duration)¹⁹ found that ICSs reduced the **rate of COPD exacerbations** compared with placebo (relative risk [RR]=0.70, 95% CI 0.58–0.84).¹⁹ It is important to note that different definitions of exacerbations were used in the RCTs, and not all RCTs to date have shown a significant reduction in COPD exacerbations with ICSs.¹⁹ Similarly, some RCTs have shown that ICSs have significant effects on **health related quality of life**, whereas others have failed to demonstrate an effect.¹³

There is insufficient evidence to establish the minimum dose of ICS required to achieve benefits. Also, there is limited experience of doses higher than 1000mcg fluticasone/day (or equivalent) and no evidence that any one ICS is superior to any other.

The systematic review¹⁹ found that, compared with placebo, ICS therapy was associated with increased rates of oropharyngeal candidiasis (RR 2.1, 95% CI 1.5–3.1) and skin bruising (RR 2.1, 95% CI 1.6–2.8). (Doses used in the RCTs were: budesonide 800–1600mcg/day, fluticasone 1000mcg/day, beclomethasone 1500–2000mcg/day and triamcinolone [not available in the UK] 1200mcg/day). There were no significant differences for cataract or fracture rates. However, follow-up was generally of short duration.¹⁹

There is no direct study evidence linking ICS use to increased fracture rates, but a subgroup analysis from one RCT has found an association between ICS use and lower bone mineral density measurements.²⁰ In addition, a small but statistically significant dose-related increase in fracture risk has been seen in a retrospective observational analysis of ICSs in

elderly patients.²¹ However, these fractures may be more related to severity of COPD rather than ICS use.²² It seems probable that ICSs will increase fracture risk if given for long enough to frail, poorly mobile people. Patients on a high ICS dose should receive a steroid card.

The only inhalers containing an ICS that are licensed for COPD are fixed combination inhalers containing a high dose ICS with a LABA. The evidence for a clear clinical advantage of combination therapy using a high dose ICS with a LABA, compared with individual components, is not substantial.^{23,24} Also, there is a risk that people with COPD are being exposed to high dose ICSs, with potential for systemic effects and little additional benefit from that of using a LABA alone. More RCTs, including comparisons of combination inhalers with their constituents as separate inhalers, are required to assess fully the place in therapy of ICS/LABA combination inhalers.^{23,24}

At the current time, the use of fixed combination inhalers should be considered on an individual basis. They may be more convenient, are claimed to aid compliance and attract only one prescription charge for patients. However, this should be balanced by the inflexibility of fixed-dose combinations, which do not allow for individual drug dose titration without the need for further items to be dispensed. This may be important with respect to adverse effects possible with the component drugs.

This Bulletin is based on work by Dr Martin Duerden, GP and Conwy Local Health Board Medical Director, North Wales.

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