# Comparing the range and costs of COPD treatments in primary care

Practice nurses should familiarise themselves with the many products available for the management of chronic obstructive pulmonary disease (COPD). **Graham Cope** outlines the treatments used in primary care, and compares cost benefits.


## ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a long-term illness caused by inflammation and tissue destruction, resulting in impaired airflow and inadequate oxygen availability during exercise. Inhalers acting on the nervous system that control the respiratory muscles are the main drug therapy used to treat COPD and are often used in combination to enhance their efficacy. Anti-inflammatory formulae are also used, but usually with long-lasting bronchoinhalers. Patients should be treated cost-effectively, but providing patient-centred care is paramount.


**Key words** | COPD | Inhalers | Medicines | Cost-effective

COPD is a significant cause of mortality and poor health, owing to the progressive and irreversible decline in lung function, with reduced airflow and an inability to supply oxygen to match the demands of exercise (Global Initiative for Chronic Obstructive Lung Disease, 2013).

The prevalence of COPD has been estimated at more than 900 000 diagnosed cases in England and Wales, but, allowing for under-diagnosis, the true prevalence is probably closer to 1.5 million, with a consequential mortality of between 25 000 and 30 000 deaths each year (Health and Safety Executive, 2014). The average cost to the NHS for each patient is estimated at £819 per year, of which 54% is for inpatient hospitalisation, 16% for GP and specialist visits, and 18% for drug and other treatments (Cope, 2015).

The chronic airflow limitation characteristic of COPD is caused by a mixture of small airway disease and parenchymal destruction (emphysema), the relative contributions of which vary from person to person. Chronic inflammation can cause structural changes and narrowing of the small airways. Destruction of the lung parenchyma – also by inflammatory processes – leads to the loss of alveolar attachments to the small airways and decreases lung elastic recoil (Vestbo et al, 2013).

## Treatment goals

The treatment goals for the management of COPD include (Vestbo et al, 2013):

- Relief of symptoms
- Improved exercise tolerance
- Prevention of disease progression
- Reduction of exacerbations and mortality, while minimising adverse effects.

To date, none of the existing medications for COPD have been shown to modify the long-term decline in lung function (Vestbo et al, 1999).

The classes of medications commonly used in treating COPD are shown in *Table 1*. They include beta$_2$-agonists (BA) and anticholinergics, which either stimulate or antagonise the neurotransmitters of the autonomic nervous system that controls the muscles involved in breathing. These drugs are frequently used in combination to enhance the actions of the individual drugs. Other drug groups commonly used include inhaled corticosteroids, which are anti-inflammatory agents and are also frequently used in combination with BA (Cope, 2015).

The choice of drug in each class depends on the availability and cost of medication, the severity of the disease and the patient's response. Each treatment regimen needs to be patient-specific as the relationship between severity of symptoms, airflow limitation, and severity of exacerbations will differ between patients (Santus et al, 2015).

## Bronchodilators

Bronchodilators are medications that increase the lung's expiratory potential as measured by the forced expiratory volume in the first second ($FEV_1$), usually by altering airway smooth muscle tone, as the improvements in expiratory flow reflect widening of the airways rather than changes in lung elastic recoil. Such medications improve emptying of the lungs, tend to reduce dynamic hyperinflation at rest and during exercise (Hay et al,

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**Table 1. Formulations and typical doses of medications for COPD**

| Drug | Inhaler (mcg) | Solution for nebuliser (mg/ml) | Oral | Vials for injection (mcg) | Duration of action (hours) |
|---|---|---|---|---|---|
| **Beta$_2$-agonists** | | | | | |
| ***Short-acting*** | | | | | |
| Fenoterol | 100–200 (MDI) | 1 | 0.05% (syrup) | | 4–6 |
| Levalbuterol | 45–90 (MDI) | 0.21, 0.42 | | | 6–8 |
| Salbutamol | 100, 200 (MDI and DPI) | 5 | 5 mg (pill)<br>0.024% (syrup) | 0.01, 0.5 | 4–6 |
| Terbutaline | 400, 500 (DPI) | | 2.5, 5 mg (pill) | | 4–6 |
| ***Long-acting*** | | | | | |
| Formoterol | 4.5–12 (MDI and DPI) | 0.01 | | | 12 |
| Arformoterol | | 0.0075 | | | 12 |
| Indacaterol | 75–300 (dpi) | | | | 24 |
| Salmeterol | 25–50 (MDI and DPI) | | | | 12 |
| Tulobuterol | | | | 2 mg (transdermal) | 24 |
| Olodaterol | 5 (SMI) | | | | 24 |
| **Anticholinergics** | | | | | |
| ***Short-acting*** | | | | | |
| Ipratropium bromide | 20, 40 (MDI) | 0.25–0.5 | | | 6–8 |
| Oxitropium bromide | 100 (MDI) | 1.5 | | | 7–9 |
| ***Long-acting*** | | | | | |
| Aclidinium bromide | 322 (DPI) | 0.25–0.5 | | | 12 |
| Glycopyrronium bromide | 44 (DPI) | | | | 24 |
| Tiotropium | 18 (DPI), 5 (SMI) | | | | 24 |
| Umeclidinium | 62.5 (DPI) | | | | 24 |
| **Combination short-acting beta$_2$-agonist plus anticholinergic in one inhaler** | | | | | |
| Fenoterol/ ipratropium | 200/80 (MDI) | 1.25/0.5 | | | 6 |
| Salbutamol/ ipratropium | 100/20 (SMI) | | | | 6–8 |
| **Combination long-acting antimuscarinic agent and long-acting beta$_2$-agonist in one inhaler** | | | | | |
| Tiotropium/ olodaterol | 2.5/2.5 (MDI) | 1.25/0.5 | | | 24 |

1992), and improve exercise performance. Bronchodilator medications are given on an 'as-needed' basis or at regular intervals, to prevent or reduce symptoms (Higgins et al, 1991).

## Beta$_2$-agonists

The principal role of BAs is to relax airway smooth muscle by stimulating beta$_2$-adrenergic receptors; this produces functional antagonism to bronchoconstriction.

**Table 1. (continued)**

| Drug | Inhaler (mcg) | Solution for nebuliser (mg/ml) | Oral | Vials for injection (mcg) | Duration of action (hours) |
|---|---|---|---|---|---|
| **Combination short-acting beta2-agonist plus anticholinergic in one inhaler** | | | | | |
| Formoterol/ aclidinium | 12/340 (DPI) | | | | 12 |
| Indacaterol/ glycopyrronium | 85/43 (DPI) | | | | 24 |
| Vilanterol/ umeclidinium | 25/62.5 (DPI) | | | | 24 |
| **Methylxanthines** | | | | | |
| Aminophylline | | | 200–600 mg (pill) | | Variable, up to 24 |
| Theophylline (SR) | | | 100–600 mg (pill) | | Variable, up to 24 |
| **Inhaled corticosteroids** | | | | | |
| Beclomethasone | 50–400 (MDI and DPI) | 0.2–0.4 | | | |
| Budesonide | 100, 200, 400 (DPI) | | | | |
| Fluticasone | 50–500 (MDI and DPI) | | | | |
| **Combination long-acting beta$_2$-agonists plus corticosteroids in one inhaler** | | | | | |
| Beclomethasone | 6/100 (MDI) | | | | |
| Formoterol/ budesonide | 4.5/160 (MDI)<br>9/320 (DPI) | | | | |
| Formoterol/ mometasone | 10/200, 10/400 (DPI) | | | | |
| Salmeterol/ fluticasone | 50/100, 250, 500 | | | | |
| Vilanterol/ fluticasone furoate | 25/100 (DPI) | | | | |
| **Systemic corticosteroids** | | | | | |
| Prednisolone | 6/100 (MDI) | | 5–60 mg (pill) | | |
| Methylprednisolone | | | 4, 8. 16 mg (pill) | | |
| **Phosphodiesterae-4 inhibitors** | | | | | |
| Roflumilast | 6/100 (MDI) | | 500 mcg (pill) | | 24 |

DPI: dry powder inhaler; MDI: metered dose inhaler; SMI: soft mist inhaler

The bronchodilator effects of short-acting beta$_2$-agonists (SABA) usually wear off within 4–6 hours (van Schayck et al, 1991). Regular and as-needed use of salbutamol and terbutaline improve $FEV_1$ and symptoms (Sestini et al, 2006). There is virtually no difference in efficacy between the two formulae, although salbutamol is less expensive (NHS Lothian, 2016) (*Table 2*).

Long-acting beta$_2$-agonists (LABA) give a duration of action of 12 hours or more. Formoterol and salmeterol significantly improve $FEV_1$ and lung volumes, dyspnea (difficult or laboured breathing), health-related quality of life and exacerbation rate (Tashkin and Fabbri, 2010). A single dose of 12 µg formoterol and 50 µg salmeterol provide comparable bronchodilation within 12 hours

(Çelik et al, 1999), and significantly reduce the numbers of patients who need hospitalisation (Kew et al, 2013). However, comparative costs are higher for salmeterol than for formoterol.

Indacaterol is a once-daily BA with a duration of action of 24 hours (Kornmann et al, 2011). This improves treatment adherence, a problem in patients with COPD due to co-morbidities and a heavy burden of drug treatments. The bronchodilator effect is significantly greater than that of formoterol and salmeterol and comparable in cost to salmeterol. Indacaterol has significant effects on breathlessness, health status and exacerbation rate (Kornmann et al, 2011) and the onset of action is similar to salmeterol (Balint et al, 2010) at a similar annual cost.

Olodaterol is a relatively new once-daily formula that is also beneficial to patients for whom treatment adherence is a problem. Olodaterol has been shown to improve lung function significantly in moderate-to-very-severe COPD, and is similar in efficacy to formoterol, with an approximate £35 per patient annual saving, compared to indacaterol and salmeterol (National Institute for Health and Care Excellence (NICE), 2015) (*Table 2*).

## Anticholinergics

The most important effect of anticholiniergic formulae in COPD is the stimulation of the muscarinic cholinergic receptors, called muscarinic agonists (MA). The bronchodilating effect of short-acting anticholinergics, such as ipratropium lasts longer than that of SABA drugs: up to eight hours after administration (Kankaanranta et al, 2015). Long-acting antimuscarinic (LAMA) formulae, such as aclidinium, have a duration of action of at least 12 hours (Jones et al, 2012), whereas tiotropium and glycopyrronium have a duration of action of more than 24 hours (Casaburi et al, 2002). Tiotropium reduces exacerbations and related hospitalisations, and improves symptoms, health status (Cheyne et al, 2013) and the effectiveness of pulmonary rehabilitation (Kesten et al, 2008).

## Combination therapy

Combining the differently acting bronchodilators enhances the individual effects with different mechanisms and durations of action, and increases the degree of bronchodilation for equivalent or lesser side effects (Vogelmeier et al, 2008). Short-term combination therapy using formoterol and indacaterol has been shown to have a bigger impact on $FEV_1$ than the single components (Tashkin et al, 2009), while combinations of SABA and anticholinergics are also superior compared to either medication alone in improving $FEV_1$ and symptoms.

Combinations of a LABA and a long-acting anticholinergic have a significant effect on treatment adherence and patient satisfaction with a significant increase in lung function (Bateman et al, 2013).

The amalgamation of olodaterol with tiotropium has been shown to improve lung function and quality of life compared to placebo and tiotropium alone, with a similar cost to other combination drugs (Singh et al, 2015). This makes it a promising new option for maintenance treatment of patients with COPD (Ramadan et al, 2015).

## Corticosteroids

### Inhaled corticosteroids

The chronic inflammation in COPD – the major cause of reduced airflow, excessive mucus production and tissue degradation – is the target for corticosteroids. However, the use of corticosteroids in patients with COPD is controversial as it provides little or no benefit and may have long-term detrimental effects; consequently, their role in the management of stable COPD is limited to specific indications, such as those with concomitant asthma (Barnes, 2010).

### Combination inhalers

An inhaled corticosteroid combined with a LABA is more effective than the individual components in improving lung function and health status, and reducing exacerbations and mortality in patients with moderate-to-severe COPD, although there is an increased risk of pneumonia (Nannini et al, 2012).

The beclomethasone and formoterol combination provides COPD patients with an equivalent improvement of dyspnoea and a faster bronchodilation in comparison to fluticasone and salmeterol combination (and may further reduce exacerbations), but this combination is probably not as effective a LAMA and LABA combination (Horita et al, 2015).

## Methylxanthines

Although the above combination describes the commonly used drug treatments, there are other classes of drug still used to treat COPD, which are usually used to supplement those combinations previously described. The methylxanthines act as non-selective phosphodiesterase inhibitors, but have also been reported to have a range

of non-bronchodilator actions (McKay et al, 1993). Theophylline, the most commonly used compound, is less effective and less well-tolerated than inhaled long-acting bronchodilators, and is not recommended as the first choice of drug; however, when used with formoterol plus budesonide, it improves dyspnea, exercise performance and pulmonary functions in moderate-to-severe COPD (Subramanian et al, 2015).

## Phosphodiesterase-4 inhibitors

An alternative anti-inflammatory approach is with phosphodiesterase-4 inhibitors, a once-daily oral medication with no direct bronchodilator activity, although it has been shown to improve $FEV_1$ in patients treated with salmeterol or tiotropium (Fabbri et al, 2009). Roflumilast is the only approved drug in this class and it reduces moderate and severe exacerbations treated with corticosteroids by 15–20% in patients with chronic bronchitis, severe-to-very-severe COPD, and a history of exacerbations. The effects on lung function are also seen when roflumilast is added to long-acting bronchodilators (Calverley et al, 2009).

## Conclusions

Inhalers that act on the nervous system, which controls the respiratory muscles, are the main drug therapy used to treat COPD. These inhalers are often used in combination to enhance their efficacy. Practice nurses should be familiar with the range and cost-effectiveness of the products used to manage COPD in primary care. **PN**

**Table 2. Annual costs for typical doses of COPD medications**

| Drug | Dosage (µg) | Annual cost |
|---|---|---|
| **Beta$_2$-agonists** | | |
| ***Short-acting*** | | |
| Salbutamol | 100 | £21.84 |
| Terbutaline | 500 | £100.76 |
| ***Short-acting*** | | |
| Formoterol | 12 | £144.08 |
| Indacaterol | 150 | £355.02 |
| Salmeterol | 25 | £355.02 |
| Olodaterol | 5 | £320.69 |
| **Anticholinergics** | | |
| ***Short-acting*** | | |
| Ipratropium bromide | 20 | £80.95 |
| ***Long-acting*** | | |
| Aclidinium bromide | 322 | £347.01 |
| Glycopyrronium bromide | 50 | £333.67 |
| Tiotropium | 5 | £406.47 |
| Umeclidinium | 65 | £333.67 |
| **Combination long-acting antimuscarinic agent and long-acting beta$_2$-agonist in one inhaler** | | |
| Tiotropium/olodaterol | 2.5/2.5 | £394.33 |

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## KEY POINTS

- Practice nurses should familiarise themselves with the range and relative costs of products used to treat COPD in primary care
- Inhalers that act on the nervous system are the main drug therapy used to treat COPD
- These inhalers are often used in combination to enhance efficacy
- Patients should be treated cost-effectively, but providing patient-centred care is paramount

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