Cost-effectiveness of treatments for COPD

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ABSTRACT

Chronic obstructive pulmonary disease is a long-term debilitating 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—often in combination to enhance their efficacy. Anti-inflammatory formulae are also used, but more likely with long-lasting bronchoinhalers.

Key Words: COPD • Inhalers • Medicines • Cost-effectiveness

Chronic obstructive pulmonary disease (COPD) is an important cause of mortality and poor health—being a progressive and irreversible decline in lung function with reduced airflow and an inability to supply oxygen to match the demands of exercise (GOLD, 2015). The prevalence of COPD has been estimated at over 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 annual cost to the NHS for each patient is estimated at £819, 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 (GOLD, 2015).

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Treatment goals

The treatment goals for the management of COPD include: relief of symptoms; improved exercise tolerance; prevention of disease progression; and reduction of exacerbations and mortality, while minimising adverse effects (GOLD, 2015). 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: beta2-agonists 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 the inhaled corticosteroids, which are anti-inflammatory agents—again they are frequently used in combination with beta2-agonists (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

Table 1. Formulations and typical doses of COPD medications (GOLD, 2015)

Drug	Inhaler (mcg)	Solution for nebulizer (mg/ml)	Oral	Vials for injection (mg)	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 & DPI)	5	5 mg (pill) 0.024%(syrup)	0.1, 0.5	4-6
Terbutaline	400, 500 (DPI)		2.5, 5 mg (pill)		4-6
Long-acting					
Formoterol	4.5-12 (MDI & DPI)	0.01			12
Arformoterol		0.0075			12
Indacaterol	75-300 (DPI)				24
Salmeterol	25-50 (MDI & DPI)				12
Tulobuterol			2 mg (transdermal)		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)				12
Glycopyrronium bromide	44 (DPI)				24
Tiotropium	18 (DPI), 5 (SMI)				24
Umeclidinium	62.5 (DPI)				24
Combination short-acting beta2-agonist plus anticholinergic in one inhaler					
Fenoterol/ Ipratropium	200/80 (MDI)	1.25/0.5			6–•
Salbutamol/ Ipratropium	100/20 (SMI)				6–8

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

the relationship between severity of symptoms, airflow limitation, and severity of exacerbations will differ between patients (Santus et al, 2015).

Bronchodilators

These are medications that increase the lung's expiratory potential as measured by the forced expiratory volume in the first second (FEV1), usually by altering airway smooth muscle tone, since 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, 1992) and improve exercise performance. Bronchodilator medications are given on an as-

Table 1 (continued).

Drug	Inhaler (mcg)	Solution for nebulizer (mg/ml)	Oral	Vials for injection (mg)	Duration of Action (hours)
Combination long-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)	240	Variable, up to 24
Theophylline (SR)			100–600 mg (pill)		Variable, up to 24
Inhaled corticosteroids					
Beclomethasone	50-400 (MDI & DPI)	0.2-0.4			
Budesonide	100, 200, 400 (DPI)	0.20. 0.25, 0.5			
Fluticasone	50-500 (MDI & DPI)				
Combination long-acting beta2-agonists plus corticosteroids in one inhaler					
Formoterol/ beclometasone	6/100 (MDI)				
Formoterol/ budesonide	4.5/160 (MDI) 9/320 (DPI)				
Formoterol/ mometasone	10/200, 10/400 (MDI)				
Salmeterol/ Fluticasone	50/100, 250, 500 (DPI)				
Vilanterol/ Fluticasone furoate	25/100 (DPI)				
Systemic corticosteroids					
Prednisone			5–60 mg (pill)		
Methyl-prednisolone			4, 8, 16 mg (pill)		
Phosphodiesterase-4 inhibitors					
Roflumilast			500 mcg (pill)		24

needed basis or at regular intervals to prevent or reduce symptoms (Higgins et al, 1991).

Beta2-agonists

The principal action of beta2-agonists (BA) is to relax airway smooth muscle by stimulating beta2-adrenergic receptors, which produces functional antagonism to bronchoconstriction. The bronchodilator effects of short-acting beta2-agonists (SABA) usually wear off within

4–6 hours (van Schayck et al, 1991). Regular and as-needed use of salbutamol and terbutaline improve FEV1 and symptoms (Sestini et al, 2006). There is virtually no difference in efficacy between the two formulae, with salbutamol being less expensive (NHS Lothian, nd) (*Table 2*).

Long-acting beta2-agonists (LABA) show duration of action of 12 hours or more. Formoterol and salmeterol significantly improve FEV1 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 provides 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 beta2-agonist with a duration of action of 24 hours (Kornmann et al, 2011)—this is a major benefit as it improves treatment adherence, which is a problem in 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, which has been shown to significantly improved lung function in moderate to very severe COPD, and similar in efficacy to formoterol with an approximate £35 annual saving per patient compared to indacaterol and salmeterol (NICE, 2015) (*Table 2*).

Table 2. Annual costs for typical doses of COPD medications (RDTC, 2015)

Drug	Dosage (µg)	Annual cost
Beta2-agonists		
Short-acting		
Salbutamol	100	£21.84
Terbutaline	500	£100.76
Long-acting		
Formoterol	12	£144.08
Indacaterol	150	£355.02
Salmeterol	25	£355.02
Olodaterol	5	£320.59
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

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 8 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, so increasing 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 FEV1 than the single components (Tashkin et al, 2009), while combinations of short-acting beta2-agonists and

Table 2 (continued).

Drug	Dosage (mcg)	Annual cost
Combination long-acting beta$_2$-agonist plus anticholinergic in one inhaler		
Formoterol/ Aclidinium (Duaklir Genuair®)	12/340	£394.33
Indacaterol/ glycopyrronium (Ultibro Breezhaler®)	85/43	£447.48
Vilanterol/ Umeclidinium (Anoro Ellipa®)	22/55	£394.33
Olodaterol tiotropium (Spiolto Respimat®)	2.5/2.5	£394.33
Inhaled corticosteroids		
Beclomethasone	200	£54.35
Budesonide	200	£64.46
Fluticasone	50	£66.01
Combination long-acting beta2-agonists plus corticosteroids in one inhaler		
Formoterol/ Beclomethasone Fostair®	6/100 (MDI)	£355.75
Formoterol/ Budesonide Symbicort®	12/400	£461.07
Salmeterol/ Fluticasone Seretide®	25/500	£496.50
Vilanterol/ Fluticasone furoate Relvar®	22/92	£337.31
Phosphodiesterase-4 inhibitors		
Roflumilast	500 mcg	£457.55

anticholinergics are also superior compared to either medication alone in improving FEV1 and symptoms. Combinations of a long-acting beta2-agonists 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, providing 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 long acting beta2-agonists 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). 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 drugs still used to treat COPD, but usually 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,

but 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 FEV1 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). BJHCM

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