

Editors: **Michael Woodward**, Head, Aged and Residential Care Services, **Stephen Campbell**, Consultant Geriatrician, **Rohan Elliott**, Clinical Pharmacist, **Graeme Vernon**, Senior Drug Information Pharmacist, **Francine Tanner**, Clinical Pharmacist, Austin Health; and **Robyn Saunders**, Consultant Pharmacist, Victoria.

# Management of Older People with Chronic Obstructive Pulmonary Disease

Vivek Malipatil, Christine F McDonald

## ABSTRACT

Worldwide, chronic obstructive pulmonary disease ranks among the most common chronic diseases and with the population ageing, its prevalence is predicted to increase. Established interventions that improve mortality include smoking cessation, and oxygen therapy in patients with significant hypoxaemia. Pharmacotherapy aims to alleviate symptoms, improve exercise tolerance and quality of life, and prevent and manage exacerbations. Although most medications are delivered via the inhaled route, adverse effects can manifest systemically. The likelihood of systemic adverse effects increases in the elderly and caution should be exercised in patients with comorbidities, such as cardiovascular disease. When indicated, combination therapies can offer superior efficacy over monotherapy. Assessment and education to ensure appropriate delivery device selection and use are integral to optimal care.

**J Pharm Pract Res 2009; 39: 302-6.**

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterised by progressive airflow limitation with symptoms of cough, breathlessness and sputum production, and an estimated prevalence of 15% in those over 65 years of age.<sup>1</sup> If airflow limitation is fully or substantially reversible, that is forced expired volume in one second (FEV<sub>1</sub>) response to bronchodilator of above 400 mL<sup>2</sup>, the older patient should be treated as for asthma.<sup>2</sup> COPD accounts for 20% of hospitalisations of older people in the US and by 2020 it is expected to rank as the third leading cause of death worldwide.<sup>3,4</sup> Available treatments can improve lung function, control symptoms, reduce severity and frequency of exacerbations, and increase exercise tolerance.<sup>5</sup> As older people are at an increased risk of adverse effects, careful consideration of treatments and modes of administration is paramount.

## RISK FACTORS AND PATHOPHYSIOLOGY

Although cigarette smoking is the major risk factor for COPD, occupational exposure and environmental pollutants are also implicated. Genetic factors are important in determining which exposed individuals will develop COPD. The best characterised of these is alpha-1-antitrypsin deficiency. In susceptible individuals, exposure to noxious gases or particles can result in

chronic inflammation with tissue injury, ineffective repair and structural changes. These changes occur in central and peripheral airways, lung parenchyma and pulmonary vasculature. Subsequent to these changes, hypoxaemia and alveolar hypoventilation can occur. Periods of increased inflammation, often triggered by infection, result in further physiological compromise and clinical exacerbations.

## DIAGNOSIS

Progressive airflow limitation is part of the ageing process and is attributed to increasing airway collapsibility. The severity of airflow limitation can be quantified by measuring the FEV<sub>1</sub> and the FEV<sub>1</sub>/forced vital capacity (FVC) ratio. Each year on average, a decline in FEV<sub>1</sub> of around 30 mL and in the FEV<sub>1</sub>/FVC value of 0.2% is noted.<sup>6</sup> Spirometry is essential for the diagnosis of COPD. The Global Initiative for Obstructive Lung Disease guidelines for management of COPD suggest a post-bronchodilator FEV<sub>1</sub>/FVC value of less than 70% is diagnostic of COPD.<sup>5</sup> Others recommend that a lower limit of normal (fifth percentile of the normal distribution range of FEV<sub>1</sub>/FVC values) should be applied.

As the FEV<sub>1</sub>/FVC value declines with age, using a fixed ratio increases the risk of over-diagnosing COPD in the elderly. However, in clinical practice this risk is tempered by factors tending towards under-diagnosis in older people. These factors include reduced perception of airflow limitation, tendency to attribute symptoms to the ageing process and lack of spirometric testing.<sup>7</sup> The Global Initiative for Obstructive Lung Disease criteria are used worldwide to differentiate COPD severity. Mild COPD is defined as a FEV<sub>1</sub> ≥ 80%; moderate 50 to 79%; and severe < 50%.<sup>5</sup> These cut-points have not been clinically validated and are mainly used because of their simplicity. The Australian and New Zealand guidelines use different cut-points and are equally valid but not as widely recognised.<sup>8</sup>

## STABLE COPD

The aims of treatment are to alleviate symptoms, improve exercise tolerance and quality of life, and to prevent and manage exacerbations.

## Smoking Cessation

The most important intervention is smoking cessation. Only smoking cessation and oxygen therapy in significant hypoxaemia have unequivocally shown improved mortality in COPD. Although the studies demonstrating these benefits were undertaken in patients under 70 years of age, the results can be extrapolated to encompass older patients.<sup>9-11</sup>

Vivek Malipatil, MBBS, Respiratory Registrar, Christine F McDonald, MBBS(Hon), PhD, FRACP, Director, Department of Respiratory and Sleep Medicine, Austin Health, Heidelberg, Victoria  
Address for correspondence: Dr Vivek Malipatil, Department of Respiratory and Sleep Medicine, Austin Health, Heidelberg Vic. 3084, Australia.  
E-mail: Vivek.Malipatil@austin.org.au

Education and counselling can assist in smoking cessation and, for nicotine dependent patients, a number of pharmacotherapies may be helpful.<sup>5</sup> These include nicotine replacement therapy, bupropion and varenicline. Caution should be exercised with these medications in patients with unstable ischaemic heart disease, seizure disorders and psychiatric illness.

### Pulmonary Rehabilitation

Pulmonary rehabilitation is integral to the management of patients with COPD. A recent study demonstrated that COPD patients over 70 years of age benefited from pulmonary rehabilitation as much as younger patients.<sup>12</sup> Therefore, it would be reasonable to recommend pulmonary rehabilitation for all patients with COPD.

### Comorbidities

The metabolic and physiological changes of ageing can influence drug efficacy and safety.<sup>6</sup> The high prevalence of comorbidities, such as cardiovascular disease and osteoporosis, in older people can directly influence the tolerability of COPD therapy.<sup>13</sup> Polypharmacy is common in the elderly and the potential for adverse effects and drug interactions is increased.<sup>14</sup> Cognitive impairment may occur as a consequence of the COPD, or from hypoxaemia or coexisting smoking-related vascular disease. Impaired cognition and fine motor skills can make it difficult for elderly patients to use their inhalers.

Few COPD trials recruit patients over 80 years of age, and often exclude patients with significant comorbidities.<sup>6</sup> In a systematic review of adverse effects from bronchodilator use, the mean age of patients in the studies cited was 58 to 69.3 years.<sup>6</sup> Data on the reduced efficacy or increased toxicity from these therapies are lacking in older COPD patients. These issues need to be considered when deciding on effective treatments that will be safe in the management of COPD in the elderly.

### Bronchodilators

Most guidelines recommend starting therapy for symptomatic relief with a short-acting bronchodilator (anticholinergic, beta agonist).<sup>5,8</sup> Depending on response and severity of symptoms, other drugs can then be added sequentially. Long-acting bronchodilators such as the anticholinergic, tiotropium, and the beta agonists, eformoterol and salmeterol, improve exercise capacity and quality of life and reduce exacerbations.<sup>15,16</sup> For moderate to severe COPD with recurrent exacerbations, combination therapy with a long-acting beta agonist and an inhaled corticosteroid can reduce exacerbations and improve quality of life.<sup>17,18</sup>

Inhaled bronchodilators remain the cornerstone of symptom control in COPD. Although reversibility testing is necessary to confirm diagnosis, response or lack of response to a bronchodilator acutely, does not predict the degree of symptomatic benefit that may be obtained by a prolonged clinical trial.

### Inhaled Beta Agonists

Subtypes of beta adrenoceptors include: beta<sub>1</sub> (cardiac muscle), beta<sub>2</sub> (airway smooth muscle) and beta<sub>3</sub> (adipose tissue). Beta<sub>2</sub> adrenoceptors are also expressed on inflammatory, epithelial, endothelial and type I and type II alveolar cells. There are structural similarities between beta<sub>1</sub> and beta<sub>2</sub> adrenoceptors. Stimulation of beta<sub>2</sub> adrenoceptors results in a cascade of intracellular events, which ultimately leads to inhibition of calcium release from intracellular stores and an influx of potassium within cells. The net effect is smooth muscle relaxation and attenuation of airway hyperreactivity.

Short-acting beta<sub>2</sub> agonists, terbutaline and salbutamol, have an onset of action that is more rapid than short-acting anticholinergics (Table 1). Long-acting beta<sub>2</sub> agonists, salmeterol and eformoterol, possess more receptor specificity than salbutamol. Eformoterol has a more rapid onset of action than salmeterol (1 to 3 min vs 10 to 30 min, respectively).

Adverse effects of beta<sub>2</sub> agonists include tremor, hypokalaemia, hypomagnesaemia and hyperglycaemia. A meta-analysis of beta agonist use in COPD reported an increased risk of cardiovascular events including tachyarrhythmias, heart failure, myocardial ischaemia and sudden cardiac death.<sup>19</sup> However, a large prospective, multicentre trial reported no significant difference in cardiovascular mortality between salmeterol and placebo in patients with a mean age of 65 years (SD 8 years).<sup>17</sup> Nonetheless, underlying cardiovascular disease is common in elderly COPD patients and these medications should be used with caution.

### Inhaled Anticholinergics

Vagal parasympathetic neural pathways innervate the airways and play a significant role in mediating airway smooth muscle tone and mucus secretion. Three muscarinic receptor subtypes have been identified in human airways. M<sub>1</sub> receptors are important in cholinergic neurotransmission. M<sub>2</sub> receptors located on postganglionic nerves have an inhibitory effect on acetylcholine release. Activation of M<sub>3</sub> receptors on smooth muscle cells contracts bronchial smooth muscle. M<sub>3</sub> receptors on submucosal glands regulate mucus secretion. As most inflammatory cells have M<sub>3</sub> receptors, acetylcholine has a role in local inflammatory responses.

**Table 1. Inhaled bronchodilators used in COPD and their doses in older people**

Drug class	Generic name	Device	Time of onset	Duration of action	Recommended dose
Short-acting beta agonist	Salbutamol	Metered dose inhaler 100 µg	1-3 min	4-6 h	1-2 puffs every 4 h
		Nebuliser 2.5 mg, 5 mg	5-15 min		
	Terbutaline	Turbuhaler 500 µg	1-3 min		1 dose every 4-6 h
Long-acting anticholinergic	Tiotropium	Handihaler 18 µg	1-2 h	≥ 24 h	1 dose daily
Short-acting anticholinergic	Ipratropium	Metered dose inhaler 18 µg	3-5 min	6 h	2-4 puffs every 6-8 h
		Nebuliser 250 µg, 500 µg			
Long-acting beta agonist	Eformoterol	Turbuhaler 6 µg, 12 µg	1-3 min	12 h	1-2 doses every 12 h
	Salmeterol	Metered dose inhaler 25 µg	10-30 min	12 h	2 puffs every 12 h
		Accuhaler 50 µg	10-30 min	12 h	1 dose every 12 h

Inhaled anticholinergics are lipid insoluble with minimal systemic absorption, and are often used first-line in COPD because of their clinical efficacy and favourable toxicity profile. Tiotropium has an affinity for all muscarinic receptors but is highly potent in antagonising M<sub>3</sub> receptors and dissociates quickly from M<sub>2</sub> receptors augmenting its bronchodilator effect. Tiotropium improves quality of life and reduces exacerbations and hospitalisation rates in COPD.<sup>15</sup> Adverse effects include dry mouth, cough and an unpleasant taste. Although urinary retention can occur the absolute frequency is low.<sup>20</sup>

Ocular effects such as pupillary dilatation and precipitation of acute angle glaucoma occur if the eyes are exposed to these drugs. This can occur with delivery of nebulised solution through a poorly fitting mask or with improper metered dose inhaler use. Some studies suggest an increased risk of cardiovascular death with inhaled anticholinergic use.<sup>9,18</sup> However, a large prospective randomised placebo-controlled study found no increase in cardiovascular events with tiotropium use.<sup>15</sup> A recent systematic review highlighted limitations in studies reporting cardiovascular outcomes and the need for prospective randomised clinical trials to enhance our understanding of the cardiovascular risk associated with inhaled anticholinergics.<sup>21</sup>

### Inhaled Corticosteroids

Inhaled corticosteroids reduce airway inflammation by altering gene transcription and protein synthesis. COPD is relatively corticosteroid resistant possibly because it is predominantly a neutrophilic inflammatory disease and is associated with reduced levels of histone deacetylase-2, a critical nuclear enzyme required to switch off inflammatory genes in COPD.<sup>22</sup> Guidelines recommend inhaled corticosteroids in patients with frequent exacerbations or those who have severe disease (FEV<sub>1</sub> < 50%) and remain symptomatic despite inhaled long-acting bronchodilator use. Clinical and physiological effects may include a reduction in symptoms and exacerbation frequency, and improvement in health status and FEV<sub>1</sub>.<sup>17</sup> Some of the large trials of inhaled corticosteroids have raised questions about data analysis and an absence of true intention-to-treat analysis in some of the studies.<sup>23</sup> Further analysis of recent studies may be needed to clarify the true role of inhaled corticosteroids in COPD.<sup>23</sup> Overall, there are few data about back-titrating of corticosteroids.

Ten to thirty per cent of the total dose of inhaled corticosteroids is systemically absorbed because of absorption from the lung. Quantifying the risk of systemic adverse effects is challenging given confounding factors such as comorbidities, oral corticosteroid use and the systemic effects of COPD. This balance of benefits versus adverse effects may be important in the elderly who are at risk of comorbidities.

Local adverse effects include oral candidiasis and dysphonia. Skin bruising is well described and the literature is conflicting regarding the risk of cataracts and osteoporosis. One study suggested an increased prevalence of cataracts, especially in patients with a lifetime beclomethasone dose exceeding 2000 mg.<sup>24</sup> This was not evident in a subgroup analysis of a randomised control trial of 6000 patients.<sup>17</sup> Similarly, while loss of bone mineral density and heightened fracture risk have been observed in some studies others have not reported such findings.<sup>25,26</sup> An increased risk of pneumonia has been noted with inhaled corticosteroid use but in the absence of an increase in pneumonia-related mortality.<sup>17</sup> Adverse effects become more prevalent when standard recommended doses are exceeded (Table 2).

### Methylxanthines

Methylxanthines inhibit phosphodiesterase and antagonise adenosine receptors. Their use has diminished because of significant adverse effects and narrow therapeutic index. Anti-inflammatory effects and increased respiratory muscle strength have also been described. Clinical benefits include lessening of dyspnoea and improved exercise tolerance.

Recent studies have suggested that low-dose methylxanthines may have immunomodulatory effects.<sup>27</sup> A randomised, placebo-controlled trial demonstrated a reduction in COPD exacerbations with a theophylline dose of 100 mg twice daily.<sup>28</sup> In this study, few of the participants were receiving concomitant drugs and it is difficult to discern the role of low-dose theophylline in addition to the drugs available in developed countries.<sup>28</sup> If theophylline is used in elderly patients, to avoid toxicity it is recommended that lower serum levels (8 to 12 mg/L; 44 to 67 μmol/L) be targeted.<sup>29</sup> Adverse effects include tachyarrhythmias, headaches, tremor, depression, gastrointestinal disturbance, behavioural disturbances and convulsions.

**Table 2. Inhaled corticosteroids used in COPD and their doses in older people**

Generic name	Device	Recommended dose	Bioequivalent dose
Beclomethasone dipropionate	Metered dose inhaler 50 μg, 100 μg Autohaler 50 μg, 100 μg	400 μg twice daily	800 μg
Budesonide	Turbuhaler 100 μg, 200 μg, 400 μg Nebuliser 0.5 mg, 1 mg	400 μg twice daily 0.5 to 1 mg twice daily	1600 to 2000 μg
Fluticasone propionate	Metered dose inhaler 50 μg, 125 μg, 250 μg Accuhaler 100 μg, 250 μg, 500 μg	500 μg twice daily	1000 μg

**Table 3. Combination inhalers used in COPD and their doses in older people**

Long-acting beta agonist/corticosteroid	Device	Recommended dose
Budesonide/eformoterol	Turbuhaler 100 μg/6 μg, 200 μg/6 μg Turbuhaler 400 μg/12 μg	1-2 doses every 12 h 1 dose every 12 h
Fluticasone/salmeterol	Metered dose inhaler 50 μg/25 μg, 125 μg/25 μg, 250 μg/25 μg* Accuhaler 100 μg/50 μg, 250 μg/50 μg,* 500 μg/50 μg*	2 puffs every 12 h 1 dose every 12 h

\*Subsidised on the Australian Pharmaceutical Benefits Scheme for chronic obstructive pulmonary disease.

### Combination Therapies

Multiple drugs are often used to manage COPD. Efficacy is similar among inhaled short-acting and long-acting beta agonists and anticholinergics. Combining bronchodilators with different mechanisms of action may achieve greater bronchodilation than using a single drug.<sup>30</sup> Long-acting beta agonists used with inhaled corticosteroids can have additive effects in achieving clinically significant outcomes (Table 3).<sup>13,31</sup> Recent studies, which included patients aged over 70 years, reported a superior improvement in pulmonary function and symptom control with triple therapy (tiotropium plus salmeterol/fluticasone) relative to each inhaler alone.<sup>32,33</sup> Using different drug classes may increase the risk of adverse effects and the risk-benefit profile for each patient needs to be considered.

### BETA-BLOCKERS

There are concerns regarding the use of beta-blockers in COPD patients with concurrent cardiovascular disease. Several studies have demonstrated that cardioselective beta<sub>1</sub>-blockers, such as metoprolol, bisoprolol and atenolol, do not induce clinically relevant bronchospasm or significantly diminish FEV<sub>1</sub> in patients with COPD.<sup>34</sup> Van Gestel et al. demonstrated that using cardioselective beta-blockers at doses above 25% of the maximum recommended daily dose is associated with a reduced 30 day (and to a lesser extent long-term) mortality in COPD patients undergoing vascular surgery.<sup>35</sup> Observational data suggest that it is safe to use beta-blockers during exacerbations in patients with cardiovascular disease and may improve survival.<sup>36</sup>

### DELIVERY DEVICES

The delivery devices used in COPD include hydro-fluoroalkane propellant-based metered dose inhalers, dry powder inhalers and nebulisers. A systematic review highlighted that there are no clinically significant differences in efficacy between the different delivery devices, provided that the devices are correctly used.<sup>37</sup> Inhaler misuse is a common phenomenon, even in patients who have been given appropriate education. This issue is especially relevant to elderly COPD patients and regular education and assessment of inhaler technique should be part of standard care.

### Metered Dose Inhalers

Appropriate metered dose inhaler use involves exhalation followed by rapid forceful inspiration that is coordinated with inhaler activation (breath hold of at least 6 seconds is recommended). Much of each dose is deposited in the oropharynx with less than 30% delivered to the lungs.<sup>38</sup> Breath-actuated metered dose inhalers overcome the problem of coordinating inspiration with aerosol release, which may be helpful in the elderly. The use of spacers allows medication inhalation with tidal breathing, increases pulmonary drug deposition and reduces oropharyngeal adverse effects.

### Dry Powder Inhalers

Dry powder inhalers are superior to metered dose inhalers in pulmonary particulate deposition. However, inspiratory flow rates sufficient to trigger the device and allow dispersion of powder at appropriate particle sizes are required. It has been estimated that 66% of patients aged over 60 years are not able to generate adequate

inspiratory flow rates.<sup>38</sup> Dry powder inhalers need to be loaded with the dose prior to use.

### Nebulisers

Nebulisers are an attractive option in older people given that their ease of use is not limited by factors such as generating adequate inspiratory flow rate or the ability to coordinate inspiration with device actuation. Nebulisers are relatively inefficient in their deposition of drug within the airways and lung. Ocular exposure to the aerosol, device contamination and transmission of airborne infection are potential complications.

### ACUTE EXACERBATIONS

COPD patients may experience acute exacerbations characterised by sustained increase in symptoms and decrease in respiratory function beyond normal day-to-day variation. Most exacerbations are precipitated by respiratory tract infections, however, in one-third of cases the aetiology remains unknown.<sup>39</sup> Frequent exacerbations are associated with worsening quality of life and reduced lung function.

### Management

Managing exacerbations involves a combination of short-acting bronchodilators, systemic corticosteroids, and when indicated, antibiotics. Supportive care, particularly in hospitalised patients, may include oxygen therapy, non-invasive ventilation and mucolytics. Although clinical trial data are scant, vaccination (pneumococcal, influenza) can prevent some infections responsible for exacerbations.<sup>40</sup> National guidelines recommend that prophylactic vaccinations should be standard therapy, particularly in patients over 65 years of age.<sup>41</sup>

During exacerbations, large doses of short-acting bronchodilators may be administered (e.g. salbutamol 100 µg inhaler up to 8 to 10 puffs, ipratropium 21 µg inhaler up to 4 to 6 puffs) with frequency titrated to clinical response or to onset of adverse effects. Nebulised therapy may be needed in patients who are tachypnoeic and have reduced inspiratory flow.

Systemic corticosteroids when used in exacerbations can lead to shorter hospital stays, as well as reduced treatment failure and relapse rates.<sup>42</sup> Oral corticosteroids (prednisolone 30 to 40 mg/day for 7 to 14 days) are preferred as they are almost 100% bioavailable and have similar efficacy to intravenous corticosteroids.<sup>43</sup> Nevertheless, intravenous corticosteroids would need to be considered in patients with severe exacerbations or if there are concerns regarding oral absorption.

COPD exacerbations with clinical signs of infection benefit from antibiotics.<sup>8</sup> Although viral infections are frequently implicated in COPD exacerbations, bacterial colonisation and infection is common. Organisms isolated from the airways of COPD patients include *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Moraxella catarrhalis*, whilst *Chlamydomphila pneumoniae* and *Mycoplasma pneumoniae* are less common. The role of antibiotics is to reduce sputum volume and purulence rather than to eradicate bacteria from the airways. Intravenous antibiotics should be considered if there are concerns regarding safety of ingesting oral antibiotics, impaired gastrointestinal absorption or in cases of pneumonia. Empirical treatment with amoxycillin or doxycycline is recommended.<sup>44</sup>

## CONCLUSION

Smoking cessation is vital when the diagnosis of COPD is made. A wealth of evidence has established that available medications are effective in achieving clinically beneficial outcomes. Although therapies are well tolerated, most pharmacological treatment studies in COPD exclude patients above 80 years of age. Risk versus benefit must be weighed when selecting medications and delivery devices for elderly patients.

**Competing interests:** None declared

## References

1. Halbert RJ, Natoli JL, Gano A, Badamgarav E, Buist AS, Mannino DM. Global burden of COPD: systematic review and meta-analysis. *Eur Respir J* 2006; 28: 523-32.
2. British Thoracic Society and Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma. A national clinical guideline. Edinburgh: Scottish Intercollegiate Guidelines Network; 2009. Available from <www.sign.ac.uk/guidelines/fulltext/101/index.html>.
3. Mannino DM. COPD: epidemiology, prevalence, morbidity and mortality, and disease heterogeneity. *Chest* 2002; 121 (suppl 5): 121S-126S.
4. Murray CJ, Lopez AD. Alternative projections of mortality and disease by cause 1990-2020: Global Burden of Disease Study. *Lancet* 1997; 349: 1498-504.
5. Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley PM, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2007; 176: 532-55.
6. Gupta P, O'Mahony MS. Potential adverse effects of bronchodilators in the treatment of airways obstruction in older people: recommendations for prescribing. *Drugs Aging* 2008; 25: 415-43.
7. Connolly MJ, Crowley JJ, Charan NB, Nielson CP, Vestal RE. Reduced subjective awareness of bronchoconstriction provoked by methacholine in elderly asthmatic and normal subjects as measured on a simple awareness scale. *Thorax* 1992; 47: 410-13.
8. McKenzie DK, Abramson M, Crockett AJ, Glasgow N, Jenkins S, McDonald CF, et al. The COPD-X plan: Australian and New Zealand guidelines for the management of chronic obstructive pulmonary disease. Bowen Hills: Australian Lung Foundation; 2008. Available from <www.copdx.org.au/guidelines/index.asp>.
9. Anthonisen NR, Connett JE, Enright PL, Manfreda J. Hospitalizations and mortality in the Lung Health Study. *Am J Respir Crit Care Med* 2002; 166: 333-9.
10. Medical Research Council Working Party. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. *Lancet* 1981; 1: 681-6.
11. Nocturnal Oxygen Therapy Trial Group. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. *Ann Intern Med* 1980; 93: 391-8.
12. Sundararajan L, Balami J, Packham S. Effectiveness of outpatient pulmonary rehabilitation in elderly patients with chronic obstructive pulmonary disease. *J Cardiopulm Rehabil Prev* 2009 (Epub ahead of print).
13. Yeo J, Karimova G, Bansal S. Co-morbidity in older patients with COPD: its impact on health service utilisation and quality of life, a community study. *Age Ageing* 2006; 35: 33-7.
14. McLean AJ, Le Conteur DG. Aging biology and geriatric clinical pharmacology. *Pharmacol Rev* 2004; 56: 163-84.
15. Tashkin DP, Celli B, Senn S, Burkhardt D, Kesten S, Menjoge S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008; 359: 1543-54.
16. Appleton, S, Jones T, Poole P, Pilotto L, Adams R, Lasserson TJ, et al. Ipratropium bromide versus long-acting beta-2 agonists for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2006; 3: CD006101.
17. Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007; 356: 775-89.
18. Wedzicha JA, Calverley PM, Seemungal TA, Hagan G, Ansari Z, Stockley RA. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. *Am J Respir Crit Care Med* 2008; 177: 19-26.
19. Salpeter SR, Ormiston TM, Salpeter EE. Cardiovascular effects of beta-agonists in patients with asthma and COPD: a meta-analysis. *Chest* 2004; 125: 2309-21.
20. Kesten S, Jara M, Wentworth C, Lanes S. Pooled clinical trial analysis of tiotropium safety. *Chest* 2006; 130: 1695-703.
21. Hilleman DE, Malesker MA, Morrow LE, Schuller D. A systematic review of the cardiovascular risk of inhaled anticholinergics in patients with COPD. *Int J Chron Obstruct Pulmon Dis* 2009; 4: 253-63.
22. Barnes PJ, Adcock IM. Glucocorticoid resistance in inflammatory diseases. *Lancet* 2009; 373: 1905-17.
23. Ford PA, Russell RE, Barnes PJ. ICS and COPD: time to clear the air. *Int J Chron Obstruct Pulmon Dis* 2009; 4: 289-90.
24. Cumming RG, Mitchell P, Leeder SR. Use of inhaled corticosteroids and the risk of cataracts. *N Engl J Med* 1997; 337: 8-14.

25. Hubbard RB, Tattersfield AE, Smith CJ, West J, Smeeth L, Fletcher A. Use of inhaled corticosteroids and the risk of fracture. *Chest* 2006; 130: 1082-8.
26. Suissa S, Baltzan M, Kremer R, Ernst P. Inhaled and nasal corticosteroid use and the risk of fracture. *Am J Respir Crit Care Med* 2004; 169: 83-8.
27. Barnes PJ. Theophylline: new perspectives for an old drug. *Am J Respir Crit Care Med* 2003; 167: 813-18.
28. Zhou Y, Wang X, Zeng X, Qiu R, Xie J, Liu S, et al. Positive benefits of theophylline in a randomized, double-blind, parallel-group, placebo-controlled study of low-dose, slow-release theophylline in the treatment of COPD for 1 year. *Respirology* 2006; 11: 603-10.
29. Fowler JB. Medication monitoring in the elderly. *Clin Lab Sci* 1995; 8: 34-8.
30. COMBIVENT Inhalation Aerosol Study Group. In chronic obstructive pulmonary disease, a combination of ipratropium and albuterol is more effective than either agent alone. An 85-day multicenter trial. *Chest* 1994; 105: 1411-19.
31. Calverley P, Pauwels R, Vestbo J, Gulsvik A, Jones P, Pride N, et al. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 2003; 361: 449-56.
32. Aaron SD, Vandemheen KL, Fergusson D, Maltais F, Bourbeau J, Goldstein R, et al. Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomised trial. *Ann Intern Med* 2007; 146: 545-55.
33. Singh D, Brooks J, Hagan G, Cahn A, O'Connor BJ. Superiority of "triple" therapy with salmeterol/fluticasone propionate and tiotropium bromide versus individual components in moderate to severe COPD. *Thorax* 2008; 63: 592-8.
34. Salpeter SR, Ormiston TM, Salpeter EE, Poole PJ, Cates CJ. Cardioselective beta-blockers for chronic obstructive pulmonary disease: a meta-analysis. *Respir Med* 2003; 97: 1094-101.
35. van Gestel YR, Hoeks SE, Sin DD, Welten GM, Schouten O, Witteveen HJ, et al. Impact of cardioselective beta-blockers on mortality in patients with chronic obstructive pulmonary disease and atherosclerosis. *Am J Respir Crit Care Med* 2008; 178: 695-700.
36. Dransfield MT, Rowe SM, Johnson JE, Bailey WC, Gerald LB. Use of beta-blockers and the risk of death in hospitalised patients with acute exacerbations of COPD. *Thorax* 2008; 63: 301-5.
37. Dolovich MB, Ahrens RC, Hess DR, Anderson P, Dhand R, Rau JL, et al. Device selection and outcomes of aerosol therapy: evidence-based guidelines. *Chest* 2005; 127: 335-71.
38. Virchow JC, Crompton GK, Dal Negro R, Pedersen S, Magnan A, Seidenberg J, et al. Importance of inhaler devices in the management of airway disease. *Respir Med* 2008; 102: 10-19.
39. Sapey E, Stockley RA. COPD exacerbations 2: aetiology. *Thorax* 2006; 61: 250-8.
40. Varkey JB, Varkey AB, Varkey B. Prophylactic vaccinations in chronic obstructive pulmonary disease: current status. *Curr Opin Pulm Med* 2009; 15: 90-9.
41. Australian Technical Advisory Group on Immunisation. The Australian immunisation handbook. 9th edition. Canberra: Department of Health and Ageing; 2008.
42. Aaron SD, Vandemheen KL, Hebert P, Dales R, Stiell IG, Ahuja J, et al. Outpatient oral prednisone after emergency treatment of chronic obstructive pulmonary disease. *N Engl J Med* 2003; 348: 2618-25.
43. de Jong YP, Uil SM, Grotjohan HP, Postma DS, Kerstjens HA, van den Berg JW. Oral or IV prednisolone in the treatment of COPD exacerbations: a randomized, controlled, double-blind study. *Chest* 2007; 132: 1741-7.
44. Therapeutic Guidelines Limited. Therapeutic guidelines: antibiotic. 12th edition. Melbourne: Therapeutic Guidelines Limited; 2004.

Received: 11 October 2009

Revisions requested after external review: 16 November 2009

Revised version received: 6 December 2009

Accepted: 8 December 2009

---

The material in this article has been accredited by SHPA as suitable for inclusion in a pharmacist's CPD plan as outlined in the **shpacpd** program. A series of questions that can assist you with evaluating your learning outcomes can be found on the SHPA web site and the answers to these questions can be lodged until December 2010 <www.shpa.org.au>. In **shpacpd** this is considered an Activity Group 2 activity: improving knowledge and skills with assessment. The number of hours will be dependent on the time taken to read the article, complete the questions and submit the answers.

---